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Medicine

Recent Advances in Clinical Hematology

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In this review we shall discuss a few of the more important aspects of clinical hematology in which significant advances have been made during the past year. These shall be confined chiefly to those advances which have an immediate clinical application.

Erythrocyte Production

It has long been known that hypoxia is a stimulus to red cell production both in animals and in man. However, the mechanism of this stimulus has not been well understood. The fact that hypoxia applied directly to the marrow cells diminished their proliferative activity indicated that hypoxia itself was not a direct stimulus, but was mediated through another mechanism. It now seems that the direct marrow stimulus is a circulating plasma factor which has been designated erythropoietin. The presence of erythroproietin can be demonstrated by injecting the plasma from hypoxic animals and measuring the increased erythrocyte production in the recipient. This erythrocyte production can be measured by the reticulocyte response or the increase in Fe^{59} uptake by the red cells. Erythropoietin derived from one species can stimulate the bone marrow of another so that the erythropoietin content of the plasma of rabbits and of man can be assayed in the rat or in the mouse. With these assay procedures it has been possible to demonstrate increased erythropoietin levels in patients with various anemias as well as in primary and secondary polycythemia. The chemical nature of the factor is unknown, and it is probable that more than one plasma factor exists. One of these is heat stable, ether soluble and is probably a lipid. It stimulates erythroblastic division but does not stimulate hemoglobin synthesis. A second factor is thermo-labile, insoluble in ether and is probably a protein or a mucoprotein. This second factor is responsible for hemoglobin production.

Erythropoietic stimulating activity has been demonstrated in serum, plasma, milk and urine. Its site of production is not known though some evidence would indicate that it may be produced in the kidney. The erythropoietic stimulating activity of cobalt would seem to be mediated through the erythropoietin system, as when cobalt is fed to animals the plasma erythropoietin level rises. It is suggested that in various forms of aplastic or hypoplastic anemia the erythropoietin level is low despite the anemia and it may be that in some of these cases there is an absence of erythropoietic stimulatory activity. It is possible that if a pure erythropoietin can be prepared these patients might respond to such a stimulus.

The Megaloblastic Anemias

Megaloblastic anemia has been described in a large number of patients following the ingestion of various anti-convulsants. These anti-convulsants include primadone, sodium phenytoin, and various barbiturates. This is an important cause of anemia in epileptics who are on long continued anti-convulsant therapy. Many such epileptics, though they do not exhibit a true megaloblastic anemia, may have some diminution in hemoglobin and an obvious macrocytosis in their peripheral blood. The anemia responds well to oral folic acid therapy. The mechanism of the production of the anemia is not well understood, and it is postulated that these substances interfere with the metabolism of folic acid and vitamin B_{12}.

Recently, the oral therapy of pernicious anemia has come into vogue with many preparations of combined B_{12} and intrinsic factor now being marketed. Most of these preparations contain a combination of B_{12} plus intrinsic factor derived from hog stomach. Following the institution of therapy there is usually a good initial response, but this is frequently followed by a decrease in hemoglobin and red cells after a period of treatment. These patients eventually develop a refractory state in which increased doses of oral therapy produce either no remission or a partial or unsatisfactory hemoglobin response. It has been found that these patients become refractory to the heterologous source of intrinsic factor and will respond again to oral therapy, if the intrinsic factor is of human origin, such as human gastric juice. This is probably due to the development of resistance to the crude hog intrinsic factor preparations. Thus, it would seem that the administration of small amounts of vitamin B_{12} with desiccated hog gastric mucosa as a source of intrinsic factor is not satisfactory maintenance therapy in pernicious anemia. There is as yet no satisfactory substitute for the parenteral injection of crystalline B_{12}.

Polycythemia

A number of cases of polycythemia associated with renal tumors as well as benign renal lesions such as hydronephrosis have been described. Benign tumors of the uterus have also been found in association with polycythemia. The cause and effect of lesion and polycythemia has been proven in these cases as the polycythemia disappears upon nephrectomy or removal of the tumor.

The association of polycythemia with cerebellar hemangioma has been recognized for some time. The basis for the polycythemia is not that of a direct vascular shunt as the shunt in these cases is small and there is no decrease in arterial oxygen saturation. It may be that the center for erythropoietin production resides in the hind brain and that a small shunt here produces local anoxia with a stimulus to an erythropoietic center in this area which in turn gives rise to increased erythropoietin production. We have been able to identify increased erythropoietin levels in one such case of cerebellar hemangioma.

The Leukemias

The diagnosis of the various leukemias usually offers little difficulty. The therapy of these diseases remains unsatisfactory and is a continuing problem. It would seem at the present time that the treatment of choice in the chronic myelocytic leukemia is radiotherapy or Myleran (Busulphan). Myleran therapy when followed with frequent blood counts offers a relatively safe method of long term control. The results in patients treated with Myleran indicate that the best method of therapy in these patients is continuous treatment. The drug should not be stopped when the signs and symptoms of the disease regress and the peripheral blood approaches normal. A small maintenance dose varying from 0.5 to 2 mgm. per day should then be instituted, and the patient maintained on the drug. The patient must be seen at regular intervals of three to four weeks to reassess the peripheral blood and adjust the dosage of the antitumor agent. Intermittent treatment has given rise to drug resistance in a relatively short period of time, and it is postulated that the mechanism here may be akin to the development of antibiotic resistant bacteria.

The treatment of chronic lymphocytic leukemia is not quite as clear cut as that of chronic myelocytic leukemia. The therapy employed is either radiation or various anti-tumor agents of which the most commonly used are nitrogen mustard or one of the oral alkylating agents such as Chlorambucil, TEM or Thio-Teppa. The least toxic of these agents is Chlorambucil, and at the present time would seem to be the agent of choice. When a refractory state develops, or, if hemolytic anemia or thrombocytopenia should supervene, then many of these patients will respond for a period of time to steroid therapy.

Leukemias in mice have been successfully treated by total body irradiation to the point of complete destruction of the leukemic marrow. The marrow can then be repopulated with normal cells derived from other mice or rats. The complete destruction of marrow results in a reduction in the immune response of the animal so that it is able to accept either a homologous or heterologous graft. Attempts have been made to duplicate these experiments in man. To date these have met with little success. The technical difficulties of total body irradiation to the point of abolishing the immune response are great. Radiation in the range of LD 50 - 100 is required. Although this offers the first hope of a "cure," many difficulties must first be overcome. It is to be hoped that some of these are not insurmountable.

Blood Coagulation

As increasing numbers of patients are receiving long term anticoagulant therapy, the long term control of such therapy has become increasingly important. When patients were receiving anticoagulants for only three or four weeks following myocardial infarction, dosage regulation could easily be adjusted with the one-stage Quick prothrombin time. Control was adequate and few hemorrhagic accidents occurred. However, now that long term anticoagulation is being used, an increasing number of patients are noted to develop hemorrhagic manifestations when the one-stage Quick prothrombin time is within a satisfactory range (20% - 30%). The reason for this is that the one-stage prothrombin time measures the factors in the second and third stages of coagulation of which the ones reduced by the coumarins are Factor VII and Prothrombin. It does not measure the factors of the first stage of coagulation. During short term anticoagulation, the factor primarily affected is Factor VII which is also one of the principal factors governing the length of the one-stage prothrombin time. Diminution in prothrombin occurs somewhat more slowly. At the same time, a reduction in Christmas factor (of the first stage of coagulation) and Stuart factor (of both first and second stages) has taken place. The one-stage Quick prothrombin time is not a reliable measure of the absolute amount of prothrombin in the plasma, it is not a good measure of Stuart factor and it does not measure Christmas factor. This means that the longer anticoagulation is carried on, the less satisfactory does the one-stage prothrombin time become as a measure of the clotting factors involved. The other tests that have been recommended are the prothrombin consumption test, the Russell Viper Venom time, and the P and P time (prothrombin-proconvertin time). As yet there is no single simple assay to replace the one-stage prothrombin time, but it is becoming

increasingly evident that a new simple, accurate procedure is required for the laboratory control of long term anticoagulant therapy. Meanwhile it must be kept in mind that these patients may bleed when the Prothrombin Time indicates a safe level of anticoagulation.

Blood Transfusion

The incidence of reactions following the infusion of whole blood is approximately 3%. These reactions are allergic, febrile and hemolytic reactions. The febrile reactions have in the past been attributed to the presence of pyrogens in the bottle and in the tubing. Though the incidence of these reactions has decreased with the use of plastic, disposable equipment, the majority of transfusion reactions are still of the febrile type. Many of these are quite severe with a temperature rise to 103° - 105°. These frequently occur in patients who have had repeated transfusions and in many, the serum contains a potent leukocyte agglutinin. This agglutinin will agglutinate and destroy the infused leukocytes. The leukocytes and platelets occurring in stored blood, though non-viable, retain their antigenic properties and so are able to stimulate an antibody response in the recipient. Following repeated transfusions the antibody in some of these patients reaches a level which is able to react with the infused cells and cause a pyrogenic reaction. When this occurs, it can be overcome by removing the buffy-coat layer (which includes both leukocytes and platelets) from above the red cell mass before the transfusion is given.

When large quantities of blood are given rapidly over a short period of time, some patients develop a hemorrhagic diathesis. This has in the past been erroneously attributed to the citrate content of the administered blood, and calcium gluconate was given in an attempt to arrest bleeding. The use of calcium gluconate in these patients is ineffective. The normal liver can metabolize the citrate present in 500 ml. of blood-ACD mixture within five to ten minutes. Moreover, bleeding manifestations due to calcium deficiency are extremely rare and, if they do occur, are always preceded by the neuromuscular effects of hypocalcemia. The reason for bleeding in these patients is frequently thrombocytopenia. The administered bank blood contains no viable platelets and where severe hemorrhage has resulted in platelet loss this deficit is not repaired. In these patients a platelet count should be done and if thrombocytopenia is present, the platelets may be replaced by the transfusion of blood in plastic bags or silicone coated bottles. In some cases if bleeding has been accompanied by shock, the hemorrhagic diathesis may be due to fibrinolysins which have been activated during the period of shock and hemorrhage. In these cases, fibrinolysins and low fibrinogen levels can be demonstrated in the peripheral blood of the patient and fibrinogen may be administered to overcome this deficit.

Klinefelter's Syndrome: Report of a Case With Some Unusual Features

Chas. G. Roland, M.D.

Klinefelter's Syndrome[2, 5, 9, 11, 17] has three more or less constant and several inconstant features. Small testes, hyalinized seminiferous tubules and azoospermia are probably present in all cases, although the syndrome may be diagnosed even if all three are not demonstrated. Gynecomastia[11], small or impalpable prostate, eunuchoid body habitus[9, 20], and the presence of sex chromatin masses in mucosal smears and tissue sections[3, 16, 18, 21] are described in varying proportions in patients with the syndrome. Urinary excretion of pituitary gonadotropins is usually increased, and the excretion of 17-ketosteroids may be subnormal.

Patients with the syndrome commonly present with one of two complaints. If a eunuchoid body habitus is present, this may be the source of the patient's concern[11]. The second, and probably more common, complaint is of infertility; it has recently been estimated at one clinic that 8.5% of all males presenting with infertility have Klinefelter's Syndrome[6]. These individuals are usually capable of coitus and a normal sex life[9, 11, 20]. Recent reports of complete spermatogenesis in isolated areas of testes from patients with the syndrome[6, 8, 23] suggest the intriguing possibility that some of these patients may be fertile. At least three cases of Klinefelter's Syndrome have been seen in the city of Winnipeg in the past few months. One of these is described elsewhere[22]. Another was seen at Deer Lodge Hospital. The third is described here. The syndrome is probably less rare than we imagine. Using various criteria, the incidence of Klinefelter's Syndrome in the male population has been suggested to be 1: 10,000[6], 1: 5,000[24], and 1: 1,000[19]. It appears to be more common in those of low than those of normal mentality[7, 19]. It is of more than academic interest to make the diagnosis, since many of the objectionable characteristics are remediable[10].

Case Report

The patient, a 25 year old Canadian, was admitted to St. Boniface Hospital on July 17, 1958. During the previous two years he had had occasional bouts of right upper quadrant abdominal pain, and had been told by another doctor that he had "liver trouble." He stated that he was also concerned about the progressive enlargement of both breasts.

On examination, he was a tall thin man with eunuchoid body habitus (Fig's. 1 and 2) and marked gynecomastia (Fig. 1). His voice was high-pitched. No facial hair was evident; the hair on his head was silky, with only slight recession of the hair line. Axillary and pubic hair was scanty, and the latter showed a typically female distribution (Fig. 3).

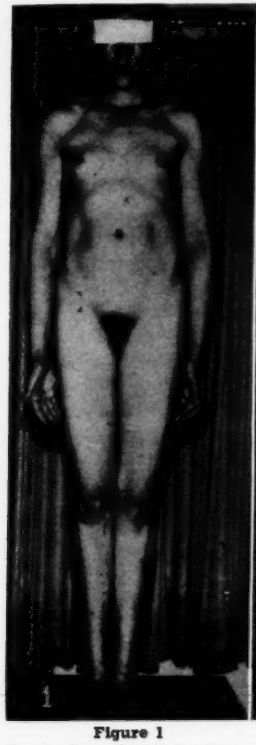

Figure 1
Front view, showing gynecomastasia, distribution of hair, and the eunuchoid body habitus.

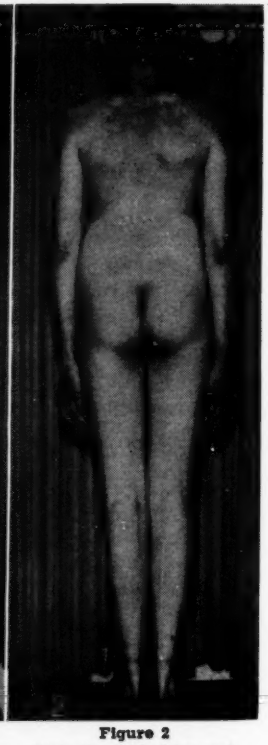

Figure 2
Note the wide hips and eunuchoid body build.

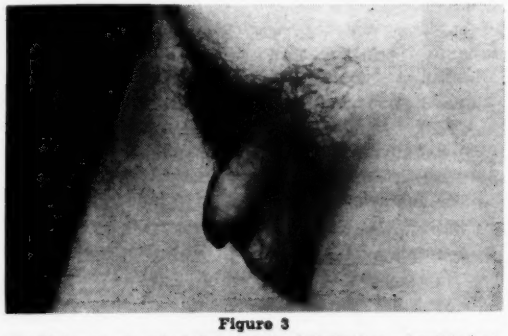

Figure 3
Genital area, showing the female distribution of pubic hair and normal appearing penis and scrotum with very small testes.

His penis and scrotum appeared normal (Fig. 3), but both testes were very small, the right being just palpable. His prostate was probably not palpable.

No abnormalities were found on examination of his heart and lungs. His blood pressure was 125/85, pulse 60 per minute. The liver edge was just palpable below the right costal margin. It was not tender. The patient weighed 158 pounds. He was 71 inches tall and had a span of 72½ inches. The distance from pubic symphysis to floor was 39 inches, while that from pubis to cranium was 32 inches. These measurements are typical of a eunuchoidal habitus.

Routine laboratory examinations of blood and urine were normal. An intravenous pyelogram and a skull roentgenogram revealed no abnormalities. Although the icterus index was elevated on a single determination (14 units) the following tests of liver function were all within normal limits: serum bilirubin; prothrombin time; serum proteins; albumin: globulin ratio; alkaline phosphatase; thymol turbidity and flocculation; cephalin cholesterol flocculation; and bromsulphalein retention.

The patient's past medical history was noncontributory. His breasts had been enlarged for many years, but during the previous eighteen months had increased markedly in size. There had been no pain or discharge associated with the enlargement. The patient also felt that his penis was abnormally small. He was concerned about his general appearance, and expressed the desire to become "more like a man."

The patient first was interested in the opposite sex about age 18. Pubic hair began to develop about this time, although growth was very light until he was about 21. He experiences erection, orgasm and ejaculation, and has had heterosexual intercourse. Facial hair has always been scanty. He did not begin to shave until age 22 or 23; he now shaves once a week.

The patient is unmarried. He has four sisters, two married and with children, and two unmarried. His only brother is unmarried at 27 years of age. So far as the patient knows, neither his father nor his brother have breast enlargement or decreased hair growth.

The findings of gynecomastia, small testes, questionably palpable prostate and eunuchoid body habitus led to the consideration of Klinefelter's Syndrome as the most likely diagnosis in this patient. Twenty-four hour urine specimens were obtained and the content of 17-ketosteroids, 17-hydroxysteroids and estrogen determined. The only estrogenic substance found in this case was estrone, of which 21.9 mcgm. were found in a 24 hour specimen. This is well above the findings in normal men, and is in the range described for adult women. The 17-keto and 17-hydroxysteroids were normal. Urinary pituitary gonadotropin estimations were not available in this case.

Smears of the patient's oral mucosa were taken and examined for the presence of sex chromatin masses. These are small distinct masses of chromatin material found adjacent to the nuclear membrane in 30-80% of the somatic cells of females[13, 14] (Fig. 4). It has been suggested that this chromatin mass is formed from the XX sex chromosome complex. In this case sex chromatin masses were found in 46% of cells examined, and the patient was reported to be "chromatin-positive." A

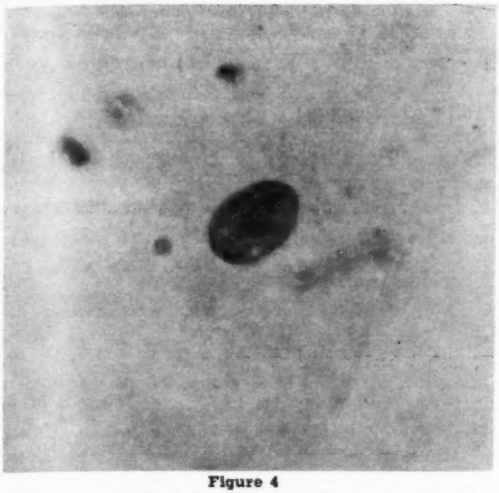

Figure 4

Nucleus of an epithelial cell obtained by scraping the oral mucosa, and showing a typical sex chromatin mass against the nuclear membrane. Cresyl echt violet. X2000.

blood smear was also examined for the presence of neutrophilic "drumsticking"[4]. Normal females have a nuclear appendage (the drumstick) in a small percentage of neutrophils, while males do not. In this patient we expected drumsticks to be present, but this was not the case.

On July 29 a testicular biopsy was performed. Microscopic examination by Dr. N. Van Wijhe was reported as showing tubules with thickened basal membranes and signs of peritubular fibrosis. The tubules were lined exclusively with Sertoli cells; no evidence of spermatogenesis was seen. Leydig cells appeared to be increased in number (Fig. 5).

Treatment was begun the day following biopsy, and consisted in a course of intramuscular injections of testosterone propionate, 25 mgm. per day for three weeks. The patient was discharged on the seventh day after operation, but continued to see his physician each day for his injection. At the conclusion of this course of treatment the patient's voice was considerably lower in pitch, there was acceleration in the rate of facial hair growth, the penis had grown in length, and erections were occurring much more frequently than prior to therapy. It is hoped that this improvement will be maintained by implanting 6-8 pellets of testosterone subcutaneously, as recommended by Heller and Nelson[10].

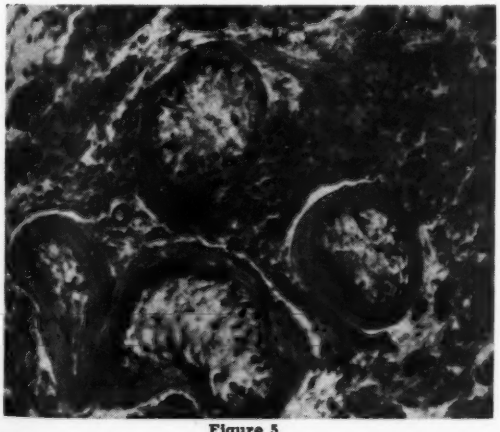

Figure 5

Photomicrograph of testicular biopsy showing hyalinized seminiferous tubules, aspermatogenesis and normal appearing Leydig cells. Hematoxylin and eosin. X300.

Discussion

The following criteria are the basis for our diagnosis of Klinefelter's Syndrome in this patient: the clinical findings of gynecomastia, small testes, questionably palpable prostate and eunuchoid body habitus; chromatin-positivity of the oral mucosal smears; and the classical[15] findings on testicular biopsy.

Some unusual features are present in this case. Oral smears and tissue sections (testis) showed sex chromatin masses in a large percentage of cells examined, indicating the chromosomal femaleness of the patient. But blood smears did not show the expected "drumsticking;" that is, the blood smears were typically male. This discordance was quite unexpected. Ashley and Jones[1] recently recorded their experience with similar discrepancies; they reported two cases in which the nuclear sex was male but the polymorph sex female. In previous reports, cited by these authors[1], several instances were described of the opposite situation. That is, the nuclear sex was female but the polymorph sex male. This case is similar. Since both oral smears and tissue sections were chromatin-positive, we accept this as the more reliable criterion of the chromosomal sex of this patient.

Urinary estrogen excretion in amounts greater than those found in normal males has rarely if ever been described in Klinefelter's Syndrome. We have found no description of such a case. In 1955 DeFelice, in a comprehensive review of the literature, commented that "no change in urinary estrogens have been noted"[5]. The significance of the abnormal amount of estrone excretion is difficult to evaluate. Leach et al[12] state that the testis accounts for 80% or more of the urinary estrogens excreted by normal men, and they feel that estrogen excretion is a more reliable and sensitive indicator of Leydig cell function than is 17-ketosteroid excretion. However, in their cases of Klinefelter's Syndrome the urinary excretion of estrogen was normal. The findings of high urinary estrogens and normal 17-ketosteroids in this patient suggest testicular (presumably Leydig cell) rather than adrenal hyperactivity.

Summary

The case report of a 25 year old "male" is recorded. The diagnosis of Klinefelter's Syndrome was made on the clinical findings of scanty hair

growth, eunuchoid body habitus, gynecomastia; small testes and questionably palpable prostate, the laboratory demonstration of chromatin-positive oral smears, and the observation, in sections from a testicular biopsy, of tubules with thickened basal membranes, aspermatogenesis, and normal or increased Leydig cells.

Two unusual features are noted: discordance in the findings by two methods of chromosomal sex determination, and the presence of estrogen excretion levels in the range found for normal females.

Acknowledgments

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Medical Research

The Effect of Dietary Supplements of Linoleic Acid on Serum Lipids

P. A. Galbraith, M.D., W. F. Perry, M.D. and R. E. Beamish, M.D.

Introduction

The studies of Beveridge[1], Ahrens[2] and others have clearly shown that hypercholesterolemia in normal as well as in atherosclerotic subjects can be reduced by ingestion of diets containing unsaturated vegetable oils. The work of Kinsell[3] further suggests that the actual amount of dietary fat consumed is not as important as the type of fat and furthermore, recent studies of this have indicated that an important factor may be the ratio of unsaturated fat to saturated fat in the diet rather than the absolute amount of fat ingested.

The frequent finding of elevated serum lipid in atherosclerosis has lead to the assumption that abnormal lipid metabolism is related in some way to the cause of atherosclerosis. Accordingly many attempts have been made to reduce serum lipids in this disease in the hopeful expectation that the course of the disease may be altered.

The use of diets containing safflower oil to prove unsaturated fatty acids chiefly linoleic acid, has been studied by various authors with conflicting results. LeRiche in 1957[4] reported that the ingestion of 14 grams of linoleic acid daily in addition to the usual diet significantly reduced serum cholesterol after 4 weeks of therapy in 20 male subjects between the ages of 33 and 60. Labecki, Wright, Thompson and Lake in 1958[5] using a much smaller daily dose of linoleic acid (2 grams) but added to a lipotropic mixture of pyridoxine, methionine and choline reported that after 30 weeks of such treatment there was some lowering of serum cholesterol and an increase in the alpha to beta lipoprotein ratio. On the other hand Perkins, Wright and Gatje[6] have reported that the administration of 35 grams of linoleic acid in the form of safflower oil to a group of young normal males for 7 weeks did not alter the serum cholesterol. In view of the lack of unanimity on the effect of linoleic acid on serum cholesterol levels it seemed of interest to study the problem further. In the present study hypercholesterolemic subjects were given linoleic acid in addition to their usual diets over a 3-week period and the serum levels of cholesterol, total serum lipid and alpha to beta lipoprotein ratio were measured before, during and after the linoleic acid treatment.

Methods

Total serum lipids, serum cholesterol and lipoprotein determinations were done weekly on 14 hypercholesterolemic atherosclerotic subjects.

From the Winnipeg General Hospital Department of Biochemistry and the Departments of Medicine and Physiology and Medical Research, University of Manitoba.

These 14 subjects consisted of 6 females and 8 males ranging in age from 36 to 74 years and all had serum cholesterol levels greater than 250 mg. %. After initial blood samples were taken the subjects were started on a commercial safflower oil emulsion containing 46% linoleic acid, 13% oleic acid, 5% saturated fats and 8% sucrose. Each patient took daily amounts of this emulsion along with their meals so as to add to their usual diet 21 grams of linoleic acid and an additional 270 calories. Prior to the study the subjects had been on diets averaging 2,000 to 2,300 calories daily and containing between 75 and 100 grams of fat, almost all of it entirely of animal origin. When on linoleic acid it was estimated that the daily fat intake consisted of 1 part unsaturated fat to 6 parts saturated fat.

All blood samples were taken in the morning, usually within an hour of breakfast. Serum cholesterol determinations were done by the method of Pearson, Stern and McGavack[7] and total serum lipids were measured according to the turbidmetric method of Kunkle[8]. Lipoproteins were stained with Oil Red O dye and analyzed densitometrically using the Sphinco Analytrol.

Results

The results for serum cholesterol, total serum lipids and beta lipoprotein before, during and after supplementing the usual diet with linoleic acid are shown in Fig. 1. From the figure it is apparent that over the period of observation only minor variations were found which proved to be not statistically significant.

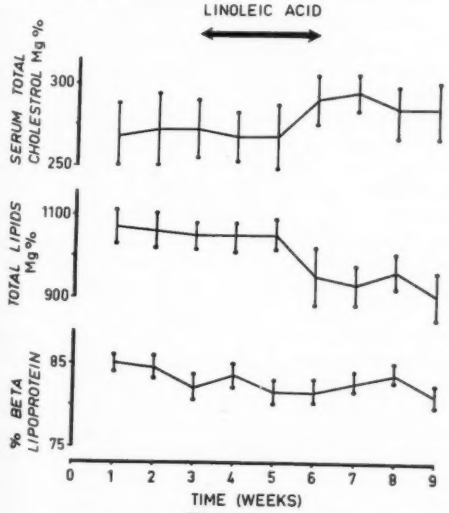

Figure 1

The Effect of Linoleic Acid on Serum Lipids

Discussion

Supplementing the usual diet of 14 hypercholesterolemic subjects with 21 grams of linoleic acid daily over a 3-week period was without significant effect on the serum lipids. Considerable variation was noted in serum cholesterol determination for most individuals from week to week although there was little change in the mean serum cholesterol of the entire group during the course of study.

The findings of the present study do not disprove the concept that supplementing the usual diet of hypercholesterolemic subjects with linoleic acid is beneficial. The recent work of Kinsell[3] has indicated that in middle aged and atherosclerotic subjects the amount of fat consumed is not as important as the ratio of the amount of saturated to unsaturated fat in the diet and that a ratio of equal amounts of saturated and unsaturated fatty acids are necessary to maintain normal serum lipids. In the present study the ratio of unsaturated and saturated fatty acids though not known precisely is calculated to be approximately 1 to 6. If Kinsell's claims are correct, it would appear that in order to obtain a 1:1 ratio of saturated to unsaturated fatty acids, it is either necessary to supplement the diet with moderate amounts of linoleic acid such as was done in the present study, but in addition drastically reduce the animal fat content of the diet, or alternatively, if a normal diet containing 80 to 100 grams of fat primarily of animal origin is consumed, to greatly increase the intake of linoleic acid to 80 - 100 grams daily. The reason for the regime adopted in this investigation was that this dose of linoleic acid used was the highest readily tolerated dose over a long period of time and in addition did not involve any drastic alteration in the patient's diet. Our results indicate that such convenient treatment for both the patient and physician is unlikely to be of any benefit.

Summary and Conclusion

Serum cholesterol, total serum lipids and beta lipoproteins were measured before, during and after a 3-week period in which the diet of 14 hypercholesterolemic subjects were supplemented with 21 grams of linoleic acid daily. No change in serum lipids attributable to the ingestion of linoleic acid could be demonstrated during this period.

Acknowledgment

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Microbiology

The Current Trend in Medical Microbiology

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In two recent numbers of the Manitoba Medical Review (January 1958 and March 1958) current developments in bacteriology and virology have been thoroughly reviewed. In the light of these articles it is interesting to explore the current trend in medical microbiology. It should be quite apparent that in recent years interest has centred more and more in the field of virology and, per contra, less and less in the field of bacteriology. This does not, of course, mean that bacteriology as a science is fading from sight. A tremendous amount of work is being done in antibiotic research and in the control, treatment and prevention of bacterial diseases, not to mention the less spectacular and more abstruse area of basic research. Nevertheless, it is obvious that, for the medical microbiologist, at least, the greatest interest lies in the developments and discoveries of virology. Virology today is in the midst of a great surge of investigation spurred on by discoveries, similar in type and import to those of its parent science, bacteriology, in the latter part of the nineteenth century.

Even a cursory inspection of the articles published in the current issues of the most popular medical journals, not to mention certain lay publications, will leave the impression that, save for the ubiquitous staphylococcus and the deceptive coliforms, all bacteria have vanished. As a matter of fact, a survey of six popular medical journals shows that articles concerning viruses, during the last nine months, outnumber those concerning bacteria by at least two to one. This preponderance of interest in matters virological merely stresses the realization that many more virus diseases exist than had heretofore been suspected: in fact, that viruses exist for which a disease entity must still be found and which Duran-Reynals[1] termed "orphans" in a "moment of conviviality."

Now why this upsurge of interest? The answer lies in advances in technology and the consequent discovery of a new field. The existence of bacteria, as independent living entities, was confirmed more than eighty years ago, but that was only when progress in techniques made it possible to see, grow and finally to isolate micro-organisms in pure culture. Of necessity, the identification of viruses lagged behind that of bacteria because, although their existence might be postulated in the light of certain disease manifestations, no techniques had been developed for their demonstration. In this regard, it may be recalled that, despite his discovery of vaccination against rabies, Pasteur[2] believed the virus with which he was concerned to be only a very small bacterium. Indeed the first inkling that viruses existed came when Beijerinck[3], reexamining some of Iwanowski's works,[4] established that the agent of tobacco mosaic disease was indeed filterable, and was an entirely new type of infective agent; **contagium vivum fluidum,** an infectious living fluid. It was not until some years later that the existence of virus disease in man became clear as a result of the work of Reed[5] and his associates upon yellow fever. Decades were yet to elapse before the actual isolation of this virus was to be achieved by Stokes, Bauer and Hudson.[6]

As with bacteria, viruses were seen sometime before they were recognized. Probably the first microscopic observation of a virus was made by John Buist[7] of Edinburgh, in 1886, who noted tiny, round objects, which he believed to be spores, in the vesicular fluids of variola and vaccinia. Some 20 years later Borrel[8], von Prowazek[9] and Paschen[10] described the similar "elementary bodies," with which their names are now associated, in fowl pox and vaccinial materials. Despite the contrivances of various ingenious methods for the microscopic examination of materials suspected of harbouring virus particles, little more could be learned concerning the actual appearance of these "elementary bodies" until the development of the electron microscope in the late 1930's[11, 12].

The isolation of viruses, in the sense of their separation from bacterial concommitants, has depended upon their ability to pass through the pores of filters impenetrable to bacterial cells. This filtrability at one time led to the organisms being referred to as the group of "filtrable viruses," a term dropped when it was discovered that not all viruses were "filtrable" nor yet all "filtrable" organisms viruses. Measurement of viruses by calculation, through measuring their sedimentation rate in the ultra-centrifuge, by their ability to pass the various porosities of the gradacol membranes developed by Elford[13], or by direct measurement from electron photomicrographs, has shown that there is no distinct gap in size between the smallest bacteria and the so-called "filtrable viruses," but that instead there is a more or less regular graduation in size from bacteria to Rickettsia to true viruses. Purification of animal viruses, in the sense of their complete separation from non-viral material, can be achieved to a great extent through ultracentrifugal procedures. The largest viruses are only slightly smaller than the Rickettsia, about 200 millimicrons for trachoma virus, or about one tenth the size of a Staphylococcus, and range down to 10 to 20 millimicrons for the very small viruses, such as Poliomyelitis and Coxsackie.

Up to the present time no one has ever succeded in cultivating viruses except in the presence of living cells, since apparently only within the living cell are the right conditions provided for their multiplication. This multiplication of virus within the cell is as yet incompletely understood, but the current concept, based upon observations made with bacteriophage, is as follows: essentially viruses consist of a core of desoxyribonucleic acid (DNA) which apparently carries the genetic material, covered by a non-specific protein outer layer, although recent studies[14] would indicate a somewhat greater complexity of constitution than this. Outside the host cell they exhibit no metabolic activity. Once inside the host cell however the picture changes. The virus leaves behind its protein outer layer upon entry into the susceptible cell to which it has become attached, the viral nucleic acid is disassembled to some extent, and then these parts are duplicated many times, recombination takes place and the newly formed viral particles leave the cell, acquiring new protein overcoats in the process. It is most likely that the energy necessary for these activities is derived from the host cell, which consequently loses some of its own metabolic activity with resultant degeneration.

This uncompromising requirement of viruses for living host cells has naturally made the task of virus research far more complex than the study of bacteria. In the early days of virus research, increased amounts of virus could be obtained only by inoculation of the desired virus into a susceptible animal. Unfortunately, most susceptible animals suffer from natural, often inapparent, viral infections; the popular white mouse has at least a half dozen such, and many a budding virologist has lost his enthusiasm, and some their lives[15], for research after dealing with a refractory ape. Yet, animal inoculation as a means of isolation and identification of viruses is still widely used, one of the commonest uses being the employment of intracerebral inoculation of suckling mice for the isolation and identification of Coxsackie virus. The use of embryonated eggs for the isolation and identification of certain viruses, particularly influenza and equine encephalitis, is also a time honored one, dating back at least to 1899 when Copeman[16] first cultivated variola virus in them, and is widely employed today thanks mainly to the methods developed by Burnet and Beveridge[17], Goodpasture[18] and others, who devised various routes of inoculation such as amniotic sac, allantoic sac, yolk sac, chorioallantoic membrane and the embryo itself. Embryonated eggs, however, have certain disadvantages as culture media. They require preliminary incubation, do not keep long in storage, have certain humidity and environmental requirements, are difficult to inoculate by any route because of their shell, which is neither adequately hard to protect them from rough handling nor yet sufficiently soft to render them readily inoculable, nor yet sufficiently translucent to enable the inoculator to see exactly what he is doing. Yet despite its failings, the embryonated egg is still the best medium we possess for the culture and identification of herpes simplex, smallpox, equine encephalitis, influenza, psittacosis and the Rickettsia.

Considering the defects inherent in living animals as culture media, it is not surprising that much effort has gone into attempts to provide a medium for viruses in which the unknown and uncontrollable living element is reduced to a minimum. Obviously, the next best thing to a synthetic medium is one which is as synthetic as possible. If viruses cannot be grown in non-living media perhaps, at least, it would be possible to grow them in a medium containing living tissue. Tissue culture seemed to be a logical answer, but the development of a satisfactory one required years of research.

Probably the immense volume of research that was carried out upon the virus of poliomyelitis has contributed most to present day virologic technique. Although as early as 1909 Landsteiner and Popper[19] had succeeded in infecting monkeys with poliomyelitis, further research was severely hampered for lack of a method of propagating the virus easily and cheaply in quantity. Monkeys were, to say the least, a nuisance, but at the time no other animal was known to be susceptible. In fact it was not until thirty years later that Armstrong[20] showed that the Lansing strain of poliomyelitis virus (type 2) could be transmitted to eastern cotton rats by intracerebral inoculation. Still later, Casals and his colleagues[21] adapted the MEFI strain to suckling mice.

In January of 1949 an article appeared in Science by Enders, Weller and Robbins[22] of the Harvard Medical School reporting their success in cultivating the Lansing strain of poliomyelitis virus in tissue cultures of various human embryonic tissues. Their experiments had been prompted by some earlier findings of Sabin and Olitsky[23] who, although they had failed to grow the virus in non-nervous tissues had noted an increase of the virus in particles of embryonic brain. Enders and his colleagues had succeeded in maintaining a series of cultures, with apparent viral increase and little loss of infectivity, for several months in tissue fragments suspended in small quantities of balanced salt solution and ox serum ultrafiltrate. Moreover they had noted another highly significant fact, namely that the infected cells of the tissues showed peculiar changes in morphology, which, although they could not be sure they were due to the virus, were highly suggestive that the virus in some way altered the cells. This "cytopathogenic effect" had been observed in 1943 by Huang[24], who had noted that his strains of western equine encephalitis virus

destroyed cells in the tissue cultures of chick embryos with which he was experimenting. He had also noted that this "cytopathogenic effect" could be neutralized by specific antiserum. Here then were two new tools to work with, not only a tissue culture method for growing the virus but a simple way of determining the type of virus present. Although it was not realized at the time, a way had been found to discover those viruses whose existence had been only a matter of speculation; viruses which were without a known disease syndrome.

In the late summer of 1947 there were several small epidemics of poliomyelitis in upstate New York. Dalldorf and Sickles[25] of the state department of health studied these in a search for the presence of possible mouse adaptable viruses. From two young boys suffering from poliomyelitis[26] they isolated a completely new and unknown virus, which when inoculated intracerebrally into suckling albino mice or hamsters, produced paralysis and death together with a widespread degeneration of the skeletal muscles. The virus did not produce paralysis in monkeys nor was it neutralized by mouse poliomyelitis sera, although it could be neutralized by pooled monkey or human globulin. Convalescent sera from the children showed neutralizing activity for it too. Obviously something new had been discovered. In a fine example of serendipity Dalldorf had stumbled upon the first member of a whole series of viruses which within the relatively short space of ten years was to grow into a group of thirty members and the limits of whose expansion is still unknown. This virus, which Dalldorf named Coxsackie after a little village where it was first found, was a member of a larger family of viruses, at that time practically unknown, now called the enteroviruses and which includes not only Coxsackie but the three types of poliomyelitis viruses and the numerous types of "orphan" or ECHO viruses.

There are at present 24 Coxsackie viruses, which have been divided into two main groups, A with 19 members and B with 5, by Dalldorf[27]. They are distinguished by the fact that group A viruses produce a generalized myositis in suckling mice, whereas group B viruses produce necrosis in the brain, liver, pancreas and embryonic fat pad but rarely focal myositis[28, 29, 30, 31].

The Coxsackie group A viruses have a number of members capable of causing the syndromes of herpangina or aseptic meningitis. A type A virus has also been found in acute, benign pericarditis[32]. It has been known for some time that group A viruses cause lesions similar to those caused by poliomyelitis virus in monkeys and in 1956 Chumakov[33] reported the isolation in Russia of a group A Coxsackie virus, known to us as type 7, from patients who apparently had clinical paralytic poliomyelitis. This was later confirmed by Ranzenhofer[33] in the U.S.A. and he suggests that this type 7 virus, which the Russians would like to call poliomyelitis virus type 4, may account for some of the cases of paralysis amongst children who have been vaccinated against poliomyelitis.

The type B viruses form a small group of only 5 immunotypes which have been pretty generally accepted as the etiologic agent of epidemic pleurodynia[34, 35] or Bornholm disease. They may also be the cause of some cases of aseptic meningitis, all five types having been isolated from cases of aseptic meningitis with rash. Coxsackie B group viruses have also been isolated from cases of acute myocarditis in infants and also from acute benign pericarditis[32]. It may be recalled that last summer there was an outbreak of a febrile illness amongst children characterized by pharyngeal lesions and vesicular exanthem, in a Toronto suburb[36]; almost three quarters of the patients gave isolates of Group A type 16 virus.

Early in 1950 Morgan, Morton and Parker[37] of the Connaught Medical Research Laboratory in Toronto, published the formula for a chemically defined mixture, called No. 199, containing nearly half that many ingredients, which was able to keep chick embryo tissues alive and growing for a month or more.

Of course other tissue culture media had been devised long before this, but they had all contained serum or other natural substrates, so this was the first successful blend of substances of known quantity and composition for the maintenance of cell life in vitro.

Tissue cultures are of two general types: (a) suspended cell and (b) fixed cell. In the first type the finely minced fragments of tissue are placed in flasks where they float or settle in a shallow layer of nutrient medium. The earlier types of tissue culture were made in hanging drops. In the second type the tissue fragments are placed upon a subtrate, often consisting of a thin layer of clotted plasma, or may be grown directly on the glass walls of the container. The popular roller tube method of culture was developed by Gey and Bang in 1939[38].

The demonstration in 1951 that certain monkey tissues[39, 40, 41, 42], notably testicular and kidney, were good for growing poliomyelitis virus in vitro, was a very important development. It was the combination now possible, of the right technique, the right medium and the right tissues that enabled Salk[43] to grow the viruses to develop his poliomyelitis vaccine.

When tissue cultures became the general medium for isolating poliomyelitis virus from stools, it was quickly noted that there were viruses other than poliomyelitis which had a cytopathogenic effect upon tissue cultures. Because so little was known about the diseases to which they belonged they were at first termed "orphan"[44] viruses and

"human enteric viruses" by others because of their derivation. These two terms were then combined in the mnemonic ECHO, that is enteric cytopathogenic human orphan group. A committee was called together in 1955[45, 46] to determine by a co-operative effort the importance of these viruses which resulted in the identification and antigenic differentiation of 13 distinct immunotypes, five of them assocated with the symptoms of aseptic meningitis but the remainder from apparently healthy individuals. The ECHO viruses can be isolated only in tissue cultures, preferably of rhesus or cynomolgus monkey kidneys, and so are distinguished from poliomyelitis virus which can be isolated in monkeys and Coxsackie which can be isolated in suckling mice. Up to the present some 19 antigenic types have been recognized and doubtless more will be in time. Unlike the coliform bacteria, which are normal inhabitants throughout life in human beings, the ECHO viruses are only transients, their incidence varying with age, time of year and socio-economic status. Of the more recently established ECHO viruses two have been associated with aseptic meningitis syndrome[47] and two with diarrhea[48].

The term "orphan" for the viruses of this group is no longer particularly apt because of the 20 current ECHO types only four have not yet been associated with a clinical syndrome. Five ECHO types have already been the cause of epidemics in various parts of the world, including an outbreak of aseptic meningitis due to types 6 and 9 recorded by Wilt[52] as occurring in Winnipeg during the summer of 1957.

This paper has been limited to members of the entero-virus group but there are numerous other viruses being isolated from other sources. The group of adenoviruses is now well established[49]. New viral agents have been found amongst the myxoviruses[50, 51], best known members of which are mumps and influenza, and because of their method of isolation, which involves the adsorption of erythrocytes onto virus infected cells in tissue cultures, they have been called the hemadsorption viruses. Doubtless we have not reached the end of the road in virology.

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Psychiatry

Review of Psychiatry — 1958

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Progress in Psychiatry in 1958 has been marked by no revolutionary developments but by advances in knowledge and changes in practice in a number of areas.

Insulin Therapy

In the past few years renewed attempts have been made to assess the results of insulin treatment. Insulin coma therapy, introduced in Vienna by Sakel in 1935, and popularized by him as a "curative" treatment for schizophrenia, followed the course of popularity of many new therapies in medicine and particularly in psychiatry. After discouraging years of treating schizophrenia with sedative baths and bromides, psychiatry was presented with a new chemical treatment which caused dramatic recovery in some cases. In the late 1930's there were developed in all progressive mental hospitals elaborate treatment regimes to administer this difficult and potentially dangerous therapy. It is clear that many patients with schizophrenia have been helped by insulin comas —either through some pharmacological action or through the psychological effect of nursing and medical care and feeding. Since adequate facilities for this therapy are available only in mental hospitals, since it usually requires several months of hospital treatment, and since it carries more than a negligible mortality, the decision as to whether a patient with early schizophrenia should be treated by other means rests on the question: "Does insulin coma therapy improve the prognosis?" It has been generally agreed that it does.

With the recent development of new techniques for the individual and group psychotherapy of schizophrenics, and the introduction of electro-convulsive treatment (about 1940) and ataraxic drugs (in 1954), the question has become—"Is there some safer and shorter method of therapy that is equally or more effective?" Some studies[1, 2, 3] designed to compare these therapies indicate that the answer is "yes." Though really adequate evidence is not at hand and Sakel published a monograph in 1954[4] re-affirming with little evidence his faith in insulin, mental hospitals are decreasingly employing insulin coma therapy in the treatment of schizophrenia.

By contrast, insulin sub-coma therapy (particularly for severe anxiety symptoms) which proved its usefulness in World War II, is increasingly used in both general and mental hospital settings.

Ataraxics and Euphoriants

New "ataraxic" and "euphorizing" drugs continue to appear as indicated in the Review[5] one year ago. Lehmann[6] has reviewed the current status of their use in practice. There are available several dozen of these agents, the indications and complications of many of which have not been adequately assessed. A useful general plan to follow in such a situation is for each practitioner to become familiar with a few of those drugs that have been in use for some years and to be cautious in employing new agents.

The psychiatric literature correctly stresses the potentially fatal complications of some of these compounds. Such complications are excessively rare, however, in distinction from the less dangerous but more common "annoying" side effects such as constipation, drowsiness, dry mouth, mild depression, etc. In general medical and psychiatric practice these are of great importance since the administration to an emotionally disturbed patient of a drug which has these undesirable effects (particularly if it causes little or no improvement in the primary symptoms) destroys rapport and makes further therapy difficult. Much research remains to be done in order to adequately establish the psychiatric indications and contra-indications for these various drugs (and indeed for other psychiatric therapies). Some patients respond in a dramatic and continuing way to a given therapy, whereas others with apparently similar illness are unchanged or worse. This reflects insufficient knowledge of the causative factors operative in each illness, and thus our inadequate etiological categorization of them. There is, however, clearly some fundamental difference between the emotional depression that responds dramatically to electro-convulsive therapy and not to Iproniazid, and the one that clears only with the use of the latter therapy.

"Direct Analysis"

The report of Horwitz and his group[7] on the follow-up of cases of schizophrenia treated by "direct analysis" by Rosen was first presented to the American Psychiatric Association Meeting in the summer of 1957. Rosen's report in the Psychiatric Quarterly in 1947[8] and his book "Direct Analysis" in 1952[9] described his experience in curing all of 37 cases treated. His method was intensive psychotherapy over several months often involving a number of hours daily and the "interpretation" to the patient directly the meaning of his psychotic productions. Rosen's publications resulted in attempts on the part of others to treat schizophrenia in a similar manner, and to the beginning of a "movement" in psychiatry to adopt this form of treatment. In showing clearly that this therapy does not indeed alter the course of the disease, Horwitz's group stress the need for caution in adopting new therapies on the basis of one worker's reports.

The Therapeutic Community

The work of Maxwell Jones[10] on the "therapeutic community" has led to a renewed interest in the use of group psychotherapy methods in psychiatric hospitals — particularly with chronically ill patients in mental hospitals. There is no doubt that this procedure assists patient management, and efforts[11] are being made to describe objectively and measure the procedure so that therapeutic results can be assessed.

Psychological Response to Disaster

In the field of community psychiatry, the studies of Tyhurst[12] and others[13] on the psychological response to disaster has been followed by useful on-the-spot studies by psychiatrists particularly at the Springhill Mine Disasters. These will doubtless lead to helpful assessments of the role of the psychiatrist and other physicians in preventing and treating disrupting patterns of behaviour—particularly panic. The usual or "normal" types of response to gross stress are being established as well as and the importance of certain measures in preventing more pathological behaviour. Important preventives are education and preparation for disaster, maintaining communication between the disabled and their families and allowing "talking out" of fears with sufficient maintenance of communication between the authorities and others so that rumor is kept to a minimum.

Publications

Two new general texts have been published—the eighth edition of Henderson & Gillespie's "A Textbook of Psychiatry" and the fifth edition of Noyes and Kolb's "Modern Clinical Psychiatry." The latter, in which Dr. Kolb participates as a co-author for the first time, is a thorough revision of an old and excellent text.

There are a number of recent books on group psychotherapy, some of which are available in the medical library[14, 15].

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Paediatrics

Vaccine Versus Virus
Thoughts on the Present Status of Salk Vaccine

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Introduction

The present poliomyelitis outbreak in this Province has again focused attention on the use of Salk Vaccine*.

My object in writing this paper is to discuss the factors which influence the efficacy of such vaccination and to try and answer some of the numerous queries that have been raised on the degree and duration of protection so acquired.

This paper is not intended to imply that the use of Salk Vaccine is capable of controlling a poliomyelitis epidemic, neither does it suggest how this can be undertaken with such a preparation. As a matter of fact, for reasons that will later be discussed, Salk Vaccine has not proven to be effective in controlling an epidemic of Poliomyelitis[1], although evidence exists that such control may be obtained by the use of the newer oral poliomyelitis vaccines[2].†

Before discussing the effects and results of Salk Vaccine, it is worthwhile to outline the immunological characteristics of a naturally occurring infection by polio virus. This will enable us to compare the immunity so produced with that obtained after vaccination.

Persons who have recovered from poliomyelitis exhibit two features which help protect them from further infections by the same viruses. Their serum contains antibodies developed against the virus which can be detected for as long as 20 to 40 years afterwards[3], the immunity developed may persist longer even though sometimes antibodies are no longer detectable[4]. This indicates that failure to detect anti-bodies does not imply loss of protection.

The second feature is an interesting and important one. Once an individual recovers from an attack of poliomyelitis, it has been found that his alimentary tract is capable of inhibiting local multiplication of the virus[4]. This can be proved by the rapid disappearance of artificially fed virus from the stools of the naturally protected[5].

This inhibition of virus excretion is not attained after Salk Vaccination.[6, 7, 4]

This is the basic fact which prevents our present vaccination program from controlling a poliomyelitis outbreak. Salk vaccination does not in any way inhibit multiplication of the virus in the gut. Protracted excretion of the virus occurs. In fact, many vaccinated individuals may be asymptomatic carriers of the virus, thus further disseminating infection.

Recent studies have proven the value of the vaccine in reducing the incidence of paralytic poliomyelitis[8]. This is exemplified by the following data from the records of the Children's Hospital, Winnipeg[9].

During the month of August 1958, 30 children were admitted to the Children's Hospital, suspected of having poliomyelitis, 15 of these were paralytic cases with 2 deaths. 14 of the paralytic cases had received incomplete or no poliomyelitis vaccination, one case which had been completely vaccinated had only minimal muscle weakness which rapidly improved.

Since the value of the vaccine in preventing paralytic poliomyelitis is well accepted, one may well ask:

What constitutes safe or complete immunization?
What is the duration of the protection acquired?
Is a fourth or booster dose necessary?

The efficacy of poliomyelitis vaccination depends on the following four factors:

1. The potency of the vaccine.
2. The ability of the vaccinated subject to respond to the vaccine.
3. The timing of the injections of the vaccine.
4. The presence in the serum of the subject of poliomyelitis antibodies acquired by subclinical exposure to the virus.

The Potency of the Vaccine

The Connaught Poliomyelitis Vaccine which has been used exclusively in this Province is prepared from the same virus strains and in the same manner as the vaccine which Salk originally designed. It is of interest that the original culture fluid which Salk used was supplied by Connaught Laboratories[8]. We can therefore safely assume that any studies indicating the efficacy of Salk Vaccine would apply equally to the Connaught Vaccine.

The basic problem in the production of poliomyelitis vaccines is to retain the antigenicity of the three types of virus at the same time rendering them completely inactive. Failure to inactivate Type I virus lead to the so-called "Cutter Incident" in 1955. On the other hand, many vaccines available prior to 1955 were safe but of such low antigenicity as to be relatively ineffective for a large

*The term Salk Vaccine and Connaught Vaccine are used synonomously in this paper to represent a vaccine prepared from killed viruses, Type I (Mahoney), Type II (M.E.F.1.) and Type III (Saukett), grown in monkey kidney tissue in synthetic medium and inactivated with formalin.

†Oral vaccine is prepared from attenuated live viruses and has been under investigation since 1955. The vaccine is not commercially available at the present time.

percentage of subjects. This fault was found to result from a preservative incorporated into the vaccine and has since been overcome.

The Ability of the Vaccinated Subject to Respond to the Vaccine

The ability to respond to an antigenic stimulus varies from individual to individual. Certain circumstances are recognized which reduce an individual's capacity to respond well to antigenic stimuli, an example is Agammaglobulinemia, a rare condition and therefore one which can be discounted. It is well known that infants respond poorly to antigenic stimuli but that the ability to respond is acquired with age. This fact has always to be considered when designing infant immunization programs. A recent study carried out by English workers has shown that infants can respond to poliomyelitis vaccine as early as one week of age, that the responses are much better at six weeks and better still at 10 weeks[10]. The poor response obtained prior to 6 weeks is more likely due to immature antibody producing mechanisms than neutralization of antigen by antibodies passively acquired from the mother.

It has always been taught that vaccinations should never be carried out in the presence of acute infection. The reasons for this are firstly, one does not wish to divert antibody responses when they are mobilized to deal with specific invading organisms, and secondly (and perhaps this is a more realistic reason) that any untoward developments in the course of the infection would be attributed to the giving of the vaccine.

Evidence exists that infants as young as six weeks of age can respond satisfactorily to four stimuli given at once, namely triple antigen and poliomyelitis vaccine and that the responses to each are just as good as when the individual antigens are given separately[11]. This then would lessen the argument that vaccination is contraindicated in the presence of infections, but it would obviously be unwise to carry out any immunization procedure if the infection is a severe one, particularly in young infants.

The Timing of the Injections of the Vaccine

The accepted schedule for poliomyelitis vaccination is three 1cc injections, the second dose four to six weeks after the first dose and the third dose seven months later. The reasons for so spacing the doses are important and have a direct bearing on the duration of protection developed and therefore influence the necessity for further booster doses.

In persons who have developed a natural immunity to poliomyelitis Salk suggests there exists a state of "immunologic hyperreactivity"[12, 13]. This means that when exposed to the polio virus, these subjects can rapidly develop a high level of circulating polio antibody even if the "resting antibody level" is zero. This response occurs within 10 to 12 days. The object of vaccination is to reproduce this phenomenon.

The mode of action of the vaccine is twofold. It first stimulates the formation of polio anti-bodies and "primes" the antibody producing mechanism. Once effectively primed, this system can rapidly produce a high titre of antibody if exposed to a similar stimulus at a later date. The first two injections act as the "priming force," often one dose is enough but two injections, especially when spaced four to six weeks apart ensure good priming. In persons who respond well to the first injection, the second dose actually produces a high rise in anti-body titre simulating the picture of "immunologic hyperactivity." This is less likely to occur if the interval between the two doses is lessened but even with a shortened interval between the doses, adequate priming should still result.

The third dose is in fact a booster. It causes a hyperimmune type of response, boosting antibody levels to a tremendous degree. Although the antibody level later falls, it does not fall to undetectable levels; at least this has not yet happened in the earliest cases vaccinated by Salk in 1954[14]. Even if the anti-body level falls to zero, if "immunological hyperreactivity" persists then failure to detect polio antibodies does not mean loss of protection.

Evidence is rapidly accumulating that the initial two doses of vaccine do not result in adequate protection[9, 15]. The third (booster) dose is all important. The longer it is delayed, the better the response, hence the seven month delay. During a polio epidemic, there will be many persons who have received the two initial doses and are awaiting the third one. I think it advisable that the third dose be given to these subjects sooner than seven months after the second so as to afford a greater measure of protection when it is most needed. It is probably wise to give them a fourth dose at a later date.

The Presence in the Serum of Poliomyelitis Antibodies Prior to Vaccination

The effect of poliomyelitis immunization is greatly enhanced by the presence in the serum of naturally acquired poliomyelitis antibodies[16]. These antibodies are equivalent to the priming effect of the initial doses of the vaccine mentioned previously. When vaccine is administered to such individuals, the antibody titres obtained after 3 doses are much better than those occurring in triple negative subjects, (i.e. persons having no previous exposure to any of the 3 polio viruses).

Figures showing the response of triple negative subjects to Salk Vaccine have been given by Sunada[16]. He showed that after standard immunization with 3 doses, 73% had Type I antibody, 99% had Type 2 and 29% had Type 3. After a fourth dose the figures were 85%, 100% and 50%.

These figures might not seem encouraging when one considers that Type I polio virus is the commonest cause of clinical disease, but fortunately the story does not end here. Clinical experience has shown that the protective effect of vaccination is greater than would be expected on the basis of such figures.

In an area where polio is endemic, such as Manitoba, it is highly probable that a large percentage of the population will have some naturally acquired antibodies, especially in view of the epidemic of 1953. This fact was confirmed by Wilt in 1955[17]. He found that in a random sample of the population of Manitoba, 90% had antibodies to polio Type 1, 70% to Type 2 and 60% to Type 3 before immunization had been carried out. He also found that in the age group of 6 months to 2 years, 75% showed polio antibody. We can therefore be reassured by the fact that the presence of naturally acquired antibodies prior to vaccination in such a high percentage of the population will result in better overall responses than those obtained in triple negative subjects.

During the present poliomyelitis outbreak most of the severe cases have occurred in children under the age of six, in other words individuals who were not exposed to poliomyelitis in 1953. There have also been several cases in adults who had not been vaccinated and it would be worthwhile pursuing an investigation to ascertain if these individuals were residents of Manitoba in 1953. It is highly probable that many of them are newcomers to this part of the world.

The enhanced response to vaccination resulting from pre-existing antibodies does not apply however, to the antibody acquired by newborn infants via the cord blood from the mother. These antibody levels gradually decline during the first six months of life.

It is important to note that so far this year no cases of poliomyelitis have been reported in infants under 3 months of age but there have been three cases of paralytic poliomyelitis in the Children's Hospital in infants in the three to six months age group, with one fatality[9]. This indicates that one should not depend on passive protection of the infant beyond three months of age and that immunization should start before three months to attempt to provide a steady level of protection.

Furthermore, all expectant mothers should be immunized, firstly because of the severity of poliomyelitis in this group and secondly to ensure full protection of their offspring until they have responded to vaccination.

Discussion

Type I Polio Virus is by far the commonest causing the disease. This virus was responsible for the 1953 epidemic in Manitoba and has been isolated from cases this summer[9].

The figures given for antibody responses in triple negative individuals show only a 73% response to Type I Antigen after three doses. Wilt has shown that the percentage of triple negative persons in this area is less than 25% at two years and less than 10% above this age, hence the number of persons who would not have detectable antibody after three doses of vaccine would be closer to two or three percent. Consideration must be given to the fact that Wilt's study was carried out in the two years immediately following a severe epidemic of poliomyelitis. It is likely that the overall percentage of persons with naturally occurring Type I antibodies is now nearer to 75%. The response to Type 2 Antigen in triple negatives is almost 100% after three doses and it is known that persons with naturally acquired Type 2 antibody are protected from paralysis of Type I virus[4]. For these reasons I do not believe there is any indication for the general application of a fourth dose of vaccine at the present time.

Since the present poliomyelitis outbreak started the public have been encouraged to avail themselves of Salk vaccination. The vaccine is supplied free of charge to persons under 40 years of age. Although we cannot prevent spread of infection by vaccination, we can provide a greater measure of protection from paralytic complications. During the Massachusetts epidemic of 1954, the incidence of paralysis in persons who had received only one dose of vaccine was 63 per 100,000 of population as against 157 per 100,000 in the unvaccinated[15].

The immunologic hyperactivity concept that Salk supports should be further discussed. The view that a prompt antibody response cuts off the virus before it reaches the C.N.S. is not generally accepted. The antibody response does not occur until 7 to 12 days after exposure to the virus[5], whereas Sabin has isolated the virus from the blood of human volunteers three days after it was administered orally[4]. If the antibody response inhibits the virus before it can reach the central nervous system, then nonparalytic poliomyelitis should be just as uncommon in the vaccinated as paralytic disease. A controlled field trial in Great Britain showed that the incidence of non paralytic poliomyelitis in the vaccinated and control groups was about equal[18]. However, I do not think we have yet achieved the final answer because many cases of so called non-paralytic poliomyelitis are in fact cases of aseptic meningitis due to the Echo and Coxsackie viruses which tend to occur commonly at the same time of the year as poliomyelitis. Complete viral studies in all non-paralytic cases may ultimately show that the incidence of non-paralytic polio is in fact reduced by vaccination.

Before concluding, one further point not hitherto discussed is worthy of mention. The high incidence of bulbar poliomyelitis in persons who

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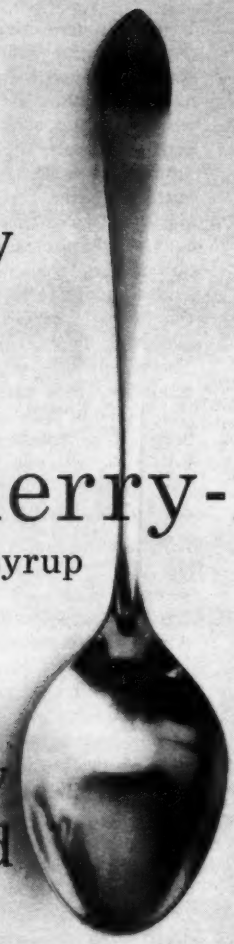

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became infected following surgery to the throat naso-pharynx is well recognized. A strong plea is made therefore for the avoidance of such operations in individuals who have not been fully immunized.

Summary

1. The factors which influence the efficacy of poliomyelitis vaccine have been reviewed.

2. The value of the vaccine in reducing the incidence of paralytic poliomyelitis has been discussed.

3. Reasons are given supporting the view that the present vaccination scheme of three doses should be adequate for this area at the present time.

4. The inability of the Salk Vaccine to control an epidemic of poliomyelitis is discussed.

5. It is suggested that the third dose of poliomyelitis vaccine be given sooner than seven months after the second whilst the present poliomyelitis outbreak continues.

6. It is recommended that surgery to the throat and naso-pharynx be restricted to completely immunized individuals.

I am grateful to Dr. H. Medovy for his advice and interest in the preparation of this paper.

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Special Paper

The Anatomy Act of Manitoba

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Introduction

The present rapid increase in the population, especially of towns and cities, creates many problems. One such problem is how to dispose of the dead; for the more people there are alive, the more there are to die. At the present time interest in cremation is growing, and so is interest in dissection. An ever-increasing number of people wish to be dissected after they are dead; but usually they do not know how to proceed to bring this about. Naturally they ask their doctor or their lawyer, only too often to find that neither professional gentleman is familiar with the legalized procedure. The main purpose of this paper is to supply this information to members of both professions, for the benefit of their patients or clients in Manitoba. This particular matter will be presented in the setting of the anatomy act of which it is a part.

Civilized societies of considerable size whose members want competent medical attention when they are sick or injured must train doctors. The centuries have made it clear that doctors must have first hand experience of the structural make-up and arrangements of the human body; they must dissect. Records of this proceeding have come down to us from the second century before Christ. Throughout the intervening centuries, whenever societies have wanted good doctors, they have had to struggle with the problem of providing dead bodies to be dissected. This has been done in two ways, legal and illegal. The historical order has been: first legal, then both, and now legal; at certain times and places both legal and illegal methods have operated simultaneously, when legal provision was inadequate.

Legal provision of the bodies of executed criminals for dissection obtained down to somewhat over a century ago; during the early years of the nineteenth century the growing need for bodies exceeded the legal supply; the latter was then supplemented by illegal methods — grave-robbing, and even murder. The passing of modern anatomy acts put an end to both the gallows and the grave as sources of anatomical material. This now consists mostly of unclaimed bodies, but with an increasing proportion of people who are dissected at their own wish.

Read to the Manitoba Medico-Legal Society, October 28, 1958.

So far as I know, on this continent anatomy is the only subject that cannot be studied without special legislation. Such legislation confers a most unique privilege upon a small group of people. But the coin has two sides: dissecting and being dissected. While many people are prepared to tolerate as a necessary evil the dissecting of other people, and other people's relatives, they are horrified at the idea of themselves or their loved ones being dissected. Though they allow their elected legislative representatives to authorize dissection, they still feel that to be dissected is a bad thing. Of course this feeling is perfectly natural, and it should be sympathetically understood by those concerned with the administration of an anatomy act.

The reasons for the popular antipathy toward dissection are twofold. First is the historical association with crime and criminals. Certainly in Manitoba this is completely irrelevant; anyone who thinks otherwise is indulging in the fantasy of living long ago and far away; this point merits no further discussion. The second reason for opposition to dissection is the notion that it involves disrespect for the dead, and that therefore it is better to be buried or cremated. Whatever historical basis there may once have been for this idea certainly no longer obtains in Manitoba, as I think you will see before I have done. A few people have religious scruples about dissection, for instance concerning its possible effect in connection with the Resurrection of the body; for discussion of this I always refer an enquirer to his or her own pastor. An increasing number of people dwell on the good aspect of dissection — on the curious circumstance that those who are dissected have the absolutely unique distinction of continuing to render service to their fellow men and women after they are dead, and a most unusual and outstanding type of service it is. People who think this way feel that it is a good thing to be dissected, and, moved by a noble and altruistic desire to do good in which they themselves will never share, they are willing to be dissected.

Manitoba Anatomy Acts

Happily, anatomical material has always been provided legally in Manitoba. The Medical College opened its doors in November, 1883, four months after the necessary legislation had been passed. This was not embodied in a separate anatomy act, but was contained in Section 141 of "An Act Respecting the Department of Agriculture, Statistics and Health," which was assented to on July 7, 1883. The first "Act Respecting the Study of Anatomy" was passed in 1899; others followed in 1902, 1913, 1937 and 1947, each being an improvement upon its predecessor. I shall not weary you with the

provisions of these successive acts, but shall proceed to discuss some points in the act under which we now operate, the act of 1947.

General Provisions of the Present Act

The Lieutenant-Governor-in-Council is authorized to appoint an inspector of anatomy and one or more sub-inspectors; but the inspector and a sub-inspector must not be "a medical practitioner or in any way directly connected with the university, other than a coroner or a medical officer in the Department of Health and Public Welfare." The Lieutenant-Governor-in-Council is also authorized to make regulations "generally for the purpose of carrying into effect this Act." Certain types of regulation are specified. The regulations made to date deal with a variety of details, especially the duties of the inspector and of the sub-inspectors.

Section 8 (3) reads "Nothing in this Act abridges or curtails the powers or authority of the coroner." This is important not only in itself, but especially when, as has been the case ever since the passing of the present act, the inspector and the coroner are one and the same person.

Section 11 provides that "An authorized person to whom a body is delivered under this Act may embalm the body upon receipt thereof, but shall keep and preserve the body otherwise intact for a period of not less than twenty-eight days." So far the only "authorized person" in the province is the University of Manitoba.

Section 13 requires that the remains of a body obtained under the act be properly interred; and Regulation 9 specifies that "the interment shall include a religious service; and, where the. . . person responsible for the interment, knows or can readily ascertain the religion of the person whose body is to be interred, the interment shall be conducted by a minister, clergyman, priest, or other officer or person authorized to conduct burial services, according to the rites of that religion."

We regard this matter of funerals as of the greatest importance. During dissection all the major remains of each person are carefully kept together, and are buried during the following summer. The university purchases plots in the appropriate cemeteries. The remains of four people, suitably segregated and labelled, are buried in each coffin, bearing the names of the four on the outside. The university (which pays all the expenses), sends a wreath of flowers for each coffin. The sexes are buried separately. The funerals are attended by most of our staff, by university officials, the inspector and one or more sub-inspectors, some students, and occasionally relatives of some of the deceased. On a sunny morning in early June, say in Brookside Cemetery, with the trees lovely in their fresh green foliage and the birds pouring forth their spring songs, the several open graves, each with its coffin and flowers beside it, the three or four clergymen, and the little bare-headed group gathered round, all make a scene of singular impressiveness. The clergy rise to the unusual occasion, often with words of appropriate beauty, for they sense the sincerity with which we pay our last respects to those whom (with a few exceptions) we never knew in life. Here in Manitoba there is no basis whatever for the expression "to be dissected instead of being buried," and the notion of disrespect for the dead surely needs no further refutation.

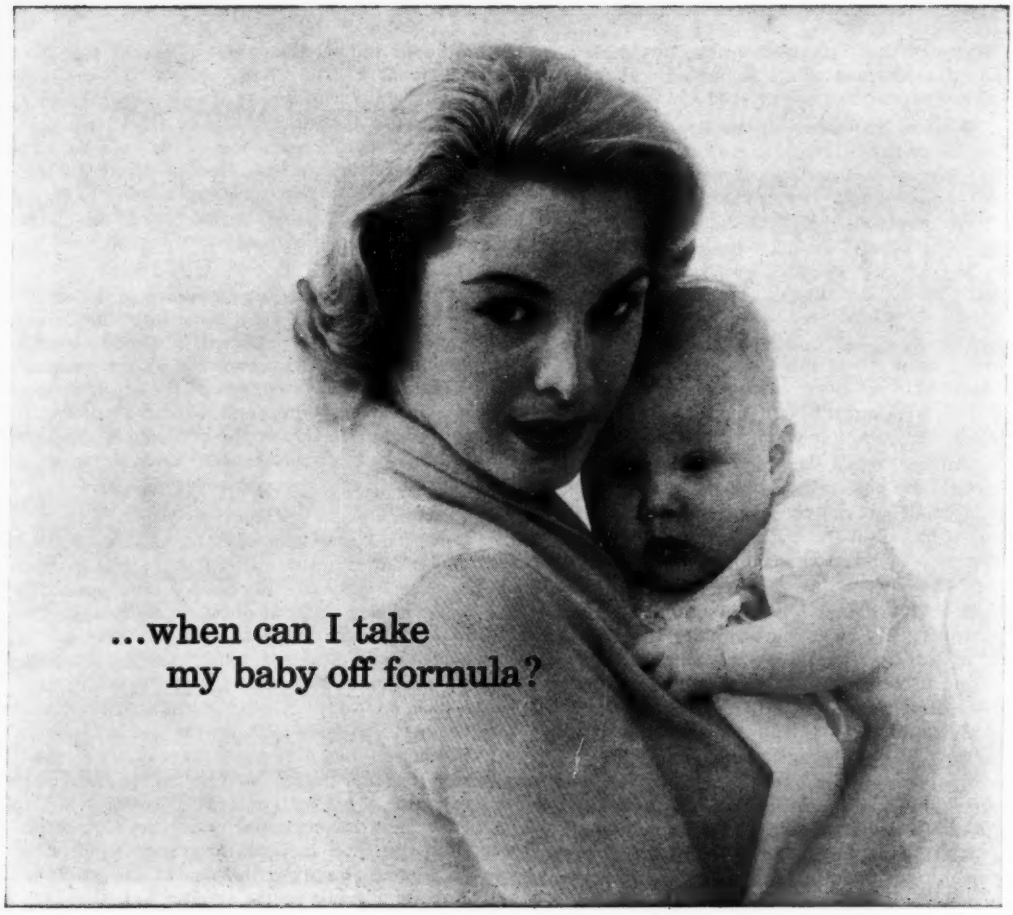
One general principle embodied in the act is that decisions as to who shall come to us and who shall leave us (by being claimed) are made by the inspector or a sub-inspector, not by the anatomists.

These general provisions of the act apply equally to unclaimed bodies and to those coming to us voluntarily. Naturally the procedures are different in the two circumstances, and these we now consider.

Unclaimed Bodies

Section 2(e) gives a list of "preferred claimants." The act does not define this term, but its meaning is clear: these are the people who ordinarily receive a body without question, so to say. The list is so important that I am going to read it. ". . . A husband, wife, parent, child, brother, sister, grandparent, grandchild, uncle, aunt, nephew, niece, first cousin, step-father, step-mother, step-child, step-brother, step-sister, father-in-law, mother-in-law, brother-in-law, or sister-in-law of a deceased person, or the person named by the deceased as executor of his will, or a representative of the Last Post Fund incorporated under the Companies Act (Canada), and includes any such kindred of the half-blood equally with those of the whole blood." Nobody else is a preferred claimant. The following omissions from the status of preferred claimant are important: (1) a friend (whether *bona fide* or not), (2) a representative of a fraternal, religious or other organization than the Last Post Fund, and (3) an administrator appointed by the court. The significance of these exclusions will appear presently.

Section 16 requires that "Every superintendent or other head of any hospital or other institution, following the death of any person in such hospital or institution, shall immediately and diligently endeavour to find a preferred claimant therefor, and shall immediately give or send a notice of the death to any such preferred claimant so found." What then follows is, of course, the ordinary course of events — undertaker, funeral, etc. But listen to Section 17. "Where a body (a) is that of a person who dies, or (b) is under the charge or control of an undertaker, coroner, physician, or other person, if (c) the body is not claimed immediately by a preferred claimant or (d) the superintendent or other head of the hospital or institution, or the person in charge or control of the body as aforesaid, is of the opinion that the body will not be claimed, such superintendent or other head, or the person



Most doctors feel it is wisest to continue the infant's evaporated milk formula for six months, adjusting it from time to time to meet his changing needs. Evaporated milk processing makes it easier to digest than fresh milk. This is an important point, since digestive upsets and diarrheas are both more difficult to treat and potentially more serious during infancy.

During baby's important first six months, you can count on the *known digestibility* of his individual evaporated milk formula to give him basic growth protection. It is far wiser to give baby this protection than to try to turn him into an adult too early!

Carnation

"FROM CONTENTED COWS"

Optimum prescription-quality in today's trend to the individualized formula.

in such charge or control, shall immediately give notice of the death to the inspector, or to the sub-inspector of the division or section in which the death occurred," and so forth. Section 19: "(1) On receipt of a notice as provided in section 17, the inspector shall immediately give notice of the death of such person . . . to the university. (2) On receipt of notice pursuant to subsection (1), the university shall, within twenty-four hours of the receipt of such notice, notify the inspector whether or not the body is required by the university . . ." Section 21: "Where a body is not required by an authorized person and remains unclaimed, the inspector shall immedately notify the authority responsible for the burial or interment of unclaimed bodies of those facts." Section 5(1): "The body of any person which remains unclaimed by a preferred claimant . . . for a period of forty-eight hours after the death of such person, shall, at the expiration of that period, be under the control of the inspector or of the sub-inspector of the division or section within which death occurred."

Let us see what some of these provisions mean. It is illegal for the superintendent or other head of a hospital or institution (and this of course includes a nursing home), or for an undertaker, coroner, physician, landlord, or other person in charge or control of a dead body to deliver it to a friend, to a representative of a religious or fraternal organization (other than the Last Post Fund), or to an administrator appointed by the court; such a body may be delivered only to a preferred claimant. If the claimant is not on the preferred list, the death must be reported immediately to the inspector or sub-inspector of anatomy; in the absence of a preferred claimant for forty-eight hours, the body automatically comes under the control of the inspector or sub-inspector.

Of course the authority of the coroner over-rides all this. The important matter of autopsies is covered in Section 8: "No person shall perform an autopsy or post-mortem upon a body to which subsection (1) of section 5 refers, unless authorized in writing to do so by the coroner." This is not necessarily a medico-legal autopsy, even though requiring authorization by the coroner. The reason for this restriction is that, since autopsied bodies cannot be enbalmed satisfactorily for dissection, they are useless to us. In practice, if the coroner knows that we are not short of material, he readily grants such permission. Sometimes he consults us; if the autopsy seems really important, permission is granted. In some cases in which there is no urgency, the Department of Anatomy records all abnormal conditions observed during dissection, and submits a report on these to the doctor or hospital concerned; in effect, this is a delayed autopsy report; it has proved satisfactory in a number of cases. Some institutions are concerned about the effect on their autopsy statistics of unautopsied bodies coming to us; they do not seem to know that in computing their autopsy percentages they are permitted to deduct such deaths from their total; of course the fact that this was done should not be suppressed.

In connection with bodies coming to us, the procedures concerning death certificates and burial permits differ from the ordinary procedures only in necessary details.

Claims and Claimants

If a preferred claimant is located after the body has come under the control of the inspector, or even has come to the university, he (or she) must apply to the inspector who, if satisfied as to the preferred status of the claimant, immediately authorizes delivery of the body.

What about non-preferred claimants — friends, fraternal and religious organizations,administrators appointed by the court, and others? All such are required to claim the body not from the hospital or other authority, but from the inspector or sub-inspector, who in these instances has practically complete discretionary powers. One group who seem not to know this point of law are officers of Trust Companies. If a man dies intestate, and such a company is appointed by the court administrator of the estate, some officials think that one of their first duties is to give the man a funeral — because money is available for it. Of course, if there is a preferred claimant, nothing else matters, and the usual events follow. But, if there is no preferred claimant, the death must be reported to the Inspector of Anatomy, to whom the administrator must apply for the body. The inspector then exercises his discretionary powers. A very important feature of the anatomy act is that it provides that not only poor people are dissected; there is not one law for the rich and another for the poor. The most destitute preferred claimant will receive a body, no matter who pays for the funeral; while the wealthiest intestate recluse is subject to the discretion of the inspector.

Sections 9 and 12(1) require a successful claimant to defray expenses incurred by the inspector or the university or both. In the event of a successful claim for a body in our possession, the Department of Anatomy gives the claimant (or his agent) a mimeographed sheet stating precisely what he must do; the essentials are that he must present to the Department (a) written authorization from the Inspector of Anatomy, and (b) a receipt from the Comptroller of the University for reimbursement of expenses. Regarding such expenses, the case of a really destitute preferred claimant would of course be treated on its merits. Section 12(2) is very important: "If a body claimed . . . has been used for purposes of anatomical or other scientific instruction or requirements, the claimant shall accept the body in the state in which it exists at the time of delivery."

There are some further important points respecting claims. Section 6(5) specifies that "A person

claiming a body may make the claim personally or through his duly authorized agent," for example an undertaker. This facilitates action by a claimant residing at a distance. Section 6(3) affords an important right of appeal. "If the authorized person or a claimant is dissatisfied with the order or ruling of the inspector or sub-inspector, he may within two days from the date of such order or ruling, and after giving to the inspector or sub-inspector notice of his intention, so to do, apply to a police magistrate for an order directing delivery of the body to him, and the police magistrate, if he is satisfied that the claim is justified, may, in his discretion, direct that such body be delivered to the applicant, subject to such conditions as the police magistrate may impose." So far, this has not happened.

Waiver of Claim

Section 6(4): "Any person entitled to claim a body may present to the inspector or sub-inspector a duly signed and witnessed waiver or renunciation of his claim; and the body shall thereafter be deemed to be unclaimed." Waiver of claim forms are obtainable from the Department of Anatomy. The simplest situation is that in which a claimant, perhaps a remote relative, or one not particularly fond of the deceased, turns up late. Upon being informed that if he takes the body, he will have to reimburse the university in the amount of thirty dollars or more, and then pay the funeral and cemetery expenses, he (or even she) sometimes prefers just to sign a waiver of claim, keep his money, and come to the funeral. A waiver of claim could be signed by a representative of the Last Post Fund or other fraternal or religious organization, or by an executor named in a will. In the circumstances under discussion the waiver of claim is signed after the death, so that the wishes of the deceased are no more consulted than in the case of an unclaimed body.

Dissection by Consent

Now we come to the situation in which, for reasons indicated earlier, a person desires to arrange that after his death his body will be dissected. Of course my statements refer only to the Province of Manitoba.

Most people who want to do this think of doing it in their wills. Concerning the matter of a will, of course I am trespassing on legal ground, so I hope that my remarks will evoke free expression of legal opinion in the discussion. When I am consulted, I advise against including this in a will. The only point in favour of doing so is that it furnishes incontrovertible evidence that such really was the wish of the deceased. But this object can be better attained in another way, to be discussed presently, and the advantage is outweighed by several disadvantages. (1) It is my understanding that in Manitoba, as in many other jurisdictions, a person's body is not part of his estate, and is therefore not at his disposal by will. Recently some States (e.g. Michigan and California) have enacted legislation specifically legalizing such a clause in a will, but that has not been done here. (2) It seems to me unfortunate (especially since it is unnecessary) to have the validity of any part of a will open to question, because that might possibly be used in an attempt to have the entire will set aside. Even though the attempt were unsuccessful, it is undesirable that it should be made at all. (3) Even though the executors might be willing to carry out such a testamentary direction, the feelings of close relatives with no prior knowledge of the matter might be outraged, and a most undesirable situation be created. (4) Embalming by an undertaker renders a body useless for dissecting, and many wills are not read until after the funeral. Then, of course, it is too late. So putting such a clause in a will considerably reduces the likelihood of the wish of the deceased being carried out.

In Manitoba a much better method is available under the anatomy act. The disposal of a dead body is ordinarily arranged by a preferred claimant. The simplest way is for the claimant to file a waiver of claim, according to Section 6(4) of the Act.

But such a decision should be made as a result of calm deliberation, preferably while the person is in good health; a good time to do it is when a will is being drawn, because then a lawyer can advise and help in connection with both documents. It should be explained to the person that the only proper way to ensure that his or her body will be dissected is to persuade the future preferred claimant (e.g. the spouse) to agree to this. If there seems any likelihood of family dissension, the idea should be dropped; if the preferred claimant is unwilling, it *must* be dropped. Forms are obtainable from the Department of Anatomy. They include a statement of consent, to be signed by the person wishing his or her body to be dissected, and approved by the future claimant. The signed and witnessed statement furnishes evidence that this was indeed the wish of the person, and renders unnecessary the inclusion of such a clause in a will. The act requires only one copy to be presented to the inspector; but we ask that the form be filled in, signed and witnessed in triplicate, one copy to be kept for reference with the other private papers of the person, and two copies to be sent to us. One of these we keep on file, the other we forward to the inspector of anatomy, as required by the act.

Because of differences of transportation and some other matters according to whether the death occurs in Winnipeg or elsewhere in Manitoba, we have two mimeographed sheets of instructions, one concerning deaths in the city, the other concerning deaths outside; these are obtainable from our department. The question of a funeral is important. Since the body must come to us unembalmed (and of course unautopsied), a funeral service of the

usual sort is not feasible. We recommend that, if a service is desired, it take the form of a Memorial Service, without the presence of the body. If no service is desired, the death notice may simply conclude: "Funeral private," or some such phrase. I need hardly say that there should be no attempt at secrecy on the part of relatives and friends; rather should they feel proud of the attitude and desire of the deceased, and of their own co-operation therewith. Of course anybody may claim the remains of a body after it has been dissected, for the purpose of a private funeral.

Some people wish to leave their bodies "for medical research." The Department of Anatomy does not usually accept such bodies, because by so doing we should accept not only the body but also the condition, thereby committing the university to an implied contract concerning the use to be made of the body. A body coming to us by personal consent comes under the anatomy act, which authorizes us to use the body "for the purpose of anatomical or other scientific instruction or requirements." This is so worded that it may or may not include research, at our discretion. We give no undertaking to do other than obey the law.

Though the act does not say so, consent or waiver of claim may be revoked or withdrawn at any time, should either the person or the claimant change his or her mind.

Conclusion

How does the anatomy act fulfil its purpose of providing bodies? In the early years there were some difficulties, but these have gradually disappeared to the extent that the present supply of male bodies is quite sufficient. But we are still seriously short of females. Of course we do not expect so many females as males, for females are not so prone as males to lose touch with their relatives. It is interesting to note that females are well represented amongst those coming to us by their own desire; at present this is our principal source of females.

I trust that it is clear that Manitoba has an excellent Anatomy Act — much better than many others. The fact that such an act has proved satisfactory is a tribute to the man who wrote it, Mr. G. S. Rutherford. I regret that pressure of work connected with the current session of the legislature prevents him from opening the discussion of this paper from the legal side; we are fortunate that his assistant, Mr. R. H. Tallin, has kindly consented to do so.

Although the anatomy act has the force of law, the success of legislation dealing with such difficult matters depends largely on how it is interpreted and administered. The core of this act lies in the very considerable discretionary powers vested in its chief administrator, the Inspector of Anatomy. The successful operation of this act for over a decade is itself a factual tribute to the humane, tactful, patient, and even good-humoured exercise of his powers by my friend Dr. I. O. Fryer. I am delighted that he is here to lead the discussion from the medical and administrative points of view.

There are others whom I might well mention, but I shall restrict myself to just one more: our senior technician, Mr. Melville Stover, who is here this evening as my guest. For many years he carried out single handed yet with conspicuous success the highly skilled, unpleasant, and sometimes difficult procedures of embalming and caring for the bodies; I am glad to be able to say that he now has competent assistance in this. He is also very successful in making practical arrangements, often by telephone, with sundry officials, undertakers, doctors and others. His is indeed a valuable contribution to the effective working of the act.

This paper has dealt with a little-known activity of every civilized society. I hope that I have left with you the impression that in Manitoba at any rate it is not wholly a bad thing to be dissected—that from death to funeral there is no abatement of that dignity and respect that our society customarily accords to its dead, nor any lack of consideration for the living whose feelings may be involved.

Editorial

S. Vaisrub, M.D., M.R.C.P. (Lond.), F.R.C.P. (C.), F.A.C.P., Editor

Pharmacodiagnosis

The giant industry, that so lavishly fills the apothecary's shelves with medicaments and the Physician's waste paper baskets with free samples and exquisitely illustrated brochures, is not given to excessive modesty. Seldom are the big drug houses known to be self effacing or bashfully silent about the magic qualities of their products. Nor are they often found at a loss for words in defending their latest favorite against all would-be attackers. Yet, curiously, these very same establishments, so unrestrained in extolling the direct therapeutic benefits of their drugs, are surprisingly reticent about the indirect "fringe" benefits which the latter have to offer in the field of pharmacodiagnosis.

The use of drugs in diagnosis is not new. One of the oldest diagnostic "methods" was the "therapeutic trial." The latter is still employed extensively despite the availability of more precise means of disease detection. Response to thyroid in borderline myxedema, to liver in doubtful pernicious anemia, to colchicine in suspected gout often helped to confirm or rule out the tentative diagnosis. More recently, the effects of prostigmine in myasthenia gravis, of rogitine and benzodioxane in pheochromocytoma, of nalorphine in morphine narcosis have similarly served as diagnostic guides. Less specific responses to salicylates in rheumatic fever, to quinine in malaria, to nitroglycerine in angina pectoris, and many others have also aided in the establishment of diagnoses in cases with inconclusive clinical evidence. In fact, almost every form of treatment is in a sense a therapeutic test, with the failure of the expected response leading to second thoughts and often to a revision of the original diagnosis.

Closely allied to the therapeutic trial is the method whereby the diagnostic implications of a drug are looked for not in its clinical results, but in its effects on some physiologic process as reflected in laboratory data. The effect of folic acid on the reticulocytes in macrocytic anemia, of Vitamin K on the prothrombin time in biliary obstruction, of parathormone on serum calcium and phosphorus levels in hypoparathyroidism are but a few examples of this modern sophisticated variant of the therapeutic test.

Occasionally drugs are used in "provocative" tests. In the not too distant past arsenicals were given to provoke a positive Wasserman reaction in a suspect luetic with negative serology. Similarly, alcohol was administered in cases of treated gonorrhea as a "test of cure." More recently histamine has been used to provoke an acute attack in cases of histamine cephalgia, or to precipitate a hypertensive response in cases of pheochromocytoma. Curare has been used in like manner to bring about an exacerbation of myasthenia gravis.

Drugs are also being used with increasing frequency in various "loading," "tolerance," "absorption" and "saturation" tests. Insulin tolerance and insulin glucose tolerance tests in Simmond's disease, B_{12} and intrinsic factor absorption tests in pernicious anemia, iron tolerance test in iron deficiency anemia, vitamin C saturation test in avitaminosis C, and many kindred tests have often proven their worth in diagnosis.

A new vast field of pharmaco-diagnosis was opened by the recent advances in hormone therapy. One of the best known is the ACTH test in the diagnosis of Addison's disease. Based on the stimulative action of ACTH on the adrenal cortex, this test differentiates primary from secondary hypoadrenalism by the failure of ACTH to elicit in the former the normal response of increase in the excretion of 17-Ketosteroids and uric acid and decrease in the circulating eosinophils. In a similar manner the stimulative action of the thyrotrophic hormone (T S H) of the anterior pituitary on the thyroid gland may help in differentiation of primary from secondary myxedema, and the trophic effects of the gonadatrophic hormones in the differential diagnosis of primary and secondary hypogonadism.

Even more stimulating to the imagination than the "stimulative," are the "suppressive" tests involving the use of cortisone in the differential diagnosis of hyperadrenocorticism. By inhibiting the trophic action of the anterior pituitary on the adrenal cortex, the administered cortisone effects a reduction in the urinary 17-Ketosteroids in cases of adrenocortical hyperplasia or adenoma, but fails to do so in adrenal carcinomas because of the latter's independence of pituitary control.

The most recent addition to the diagnostic versatility of cortisone is its use in detecting the pre-diabetic state. Fajans & Conn (Diabetes 3: 296, 1954), and more recently Conn in his Banting Memorial Lecture (Diabetes 7: 347, 1958) reported on their studies of the results of glucose tolerance tests preceded by the administration of Cortisone in near relatives of diabetics with normal standard glucose tolerance curves. 25% of the relatives of diabetics manifested impaired carbohydrate tolerance as compared with only 2% of a control group. These finding suggest that the cortisone-glucose tolerance test may become a valuable tool in the diagnosis of early diabetes.

Such are some of the diagnostic "fringe" benefits derived from therapeutic agents. There are, of course, many others, of which, regretfully, no mention was made in this brief disquisition. Rather

than make late amends by hastily adding to the list such items as bronchodilators in pulmonary function studies, radiotherapy in tumor diagnosis, hormones in the detection of pregnancy and a few other glaring omissions the editorial pen would prefer to end on a note of cheerful generalization by referring to the future of pharmacodiagnosis—a future which appears to be promising, for it rests on the premise that therapy and diagnosis are not separate water-tight compartments, but closely interlocked disciplines destined for continuous mutual enrichment.

Letters to The Editor

Dear Editor:

The following paragraph taken from C. M. A. letter dated December 29th, 1958, was considered by the Officers to merit printing in the Review:

"Meetings of various kinds punctuate the lives of secretaries although they do not constitute our sole raison d'etre as a few of our masters, the members, seem to think. We have had our full share of such gatherings this year and I'd like to record that the highlight for me was the 50th Anniversary of the Manitoba Division which was combined with the 75th birthday of the medical school at University of Manitoba. Congratulations on a very fine performance."

The letter is signed by Dr. A. D. Kelly, General Secretary. M. T. M.

Dear Editor:

In the absence of a "Letters to the Editor" column in the January issue, I address this letter for the Editor concerning his statements in the January editorial.

It would seem to be a great pity if the Editor's statements in this editorial were to be taken literally and that we earnest practitioners of Manitoba could no longer look forward to an editorial of lightness and amusement such as occurs so often in the Manitoba Medical Review.

D. E. Yates, M.D.

Income Tax

Accurate information concerning Income Tax usually appears in the Canadian Medical Association Journal during February or March. Members are advised to consult the pages of that publication or to contact the officer in charge of professional accounts at the local income tax office.

Abstract from the Literature

The Treatment of Cirrhotic Ascites by Combined Hepatic Portal Decompression. Wm. V. McDermott, Jr. New England Journal of Medicine, Vol. 259, pp. 897.

The author, in a carefully documented case describes a new treatment (successful in this one case and five others) for cirrhotic ascites.

He points out that Eck's experimental portocaval shunt was undertaken in the hope that it might aid in the treatment of ascites in man. However, over the years the high failure rate of shunt operations for the correction of ascites provided the clinical corroboration of experimental evidence that elevated pressure in the portal bed was not the cause per se of ascites.

Experimentally it was shown that ascites could be produced by any procedure that obstructs the outflow from the liver, but not by procedures that obstruct the portal vein (ascitic fluid has the same composition as liver lymph). Other contributing factors appear to be arterio-portal communications, increased intrahepatic pressure, and increased transudation of hepatic lymph and osmotic pressure relations. Hyperaldosteronism appears to be the result, rather than the cause of altered sodium and water in the body.

On the basis that the "outflow block" concept was one of the major physiological defects an operation was devised to treat the ascites by hepatic decompression and to correct the portal hypertension at the same time. This resulted in the double end to side portocaval shunt.

The results of six cases have been excellent.

W. J. Lehmann.

Research Awards — Manitoba Heart Foundation

In its first year of operation, the Manitoba Heart Foundation granted funds in the total amount of $59,988 for medical research in cardiovascular diseases. The title and outline of each project, together with the name of the person receiving the grant are set forth hereunder.

♦

Georgina R. Hogg, M.D., Pathology Department, University of Manitoba.

"Subendocardial Fibro-elastosis."

Outline: To study the relationship of subendocardial fibro-elastosis to congenital defects, cardiac and otherwise, and to chronic anoxia.

♦

H. T. G. Strawbridge, M.D., F.R.C.P.(C), Pathology Department, University of Manitoba.

"Calcific Aortic Stenosis and Related Valvular Lesions."

Outline: To establish etiology of this condition with special reference to the role of rheumatism, non-specific degeneration and thrombosis.

♦

Walter Zingg, M.D., F.R.C.S., Department of Surgery, University of Manitoba.

"Differential Brain Cooling in Open Cardiac Surgery and following Experimental Cerebral Infarction."

Outline: It is proposed to determine if the circulation can be stopped for a period of time adequate to perform open cardiac surgery by differentially cooling the brain. It will also be attempted to determine whether the spinal cord is protected by differential cooling. The possible beneficial effect of differential brain cooling in the treatment of cerebral infarction following experimental embolism will be investigated.

♦

Professor Mark Nickerson, Ph.D., M.D., Department of Pharmacology and Therapeutics, University of Manitoba.

"A Co-ordinated Pharmacological and Physiological Investigation of Cardiovascular Responses and Functions."

Outline: This project is designed to elucidate the characteristics and mechanisms of action of cardiovascular drugs, to determine the nature of responses to pharmacological agents during periods of abnormal cardiovascular physiology and pathological physiology, and to evaluate the use of pharmacological agents in the treatment of cardiovascular disease.

Morley Cohen, M.D., Ph.D., F.R.C.S. (C), Saint Boniface Hospital.

"Experimental Production of Pulmonary Hypertension — factors influencing genesis and reversibility."

Outline: By creation of appropriate vascular shunts pulmonary vascular lesions identical with those occuring in human disorders associated with pulmonary hypertension can be produced. This usually requires 3 - 7 months. The production of those changes and their reversibility can be influenced by both physical factors (i.e., pressure, pulse character) as well as endocrine factors. It is the purpose of this study to define some of these factors with a particular view to their possible application in human cardiovascular disorders associated with pulmonary hypertension.

♦

In addition to those projects, the sum of $25,000 was provided to procure equipment for the cardio-respiratory sections of the Clinical Investigation Units of the St. Boniface, Winnipeg Children's and Winnipeg General Hospitals, under the supervision of Professor J. Doupe, M.D., M.R.C.P., Chairman of the Department of Physiology and Medical Research, University of Manitoba.

♦

The Heart Foundations of Canada have received and are now reviewing applications for Research Awards for the year commencing July 1st, 1959. Anyone wishing further information on this program, or requiring application forms should address their enquiries to the Manitoba Heart Foundation, 322 Somerset Building, Winnipeg 1.

♦

The Isaac Ray Lectureship in Medico-Legal Psychiatry

The Isaac Ray Lectureship in Medico-Legal Psychiatry will be held at the University of Manitoba on March 2nd to 5th. It will consist of three evening lectures and three afternoon discussion periods on the following topics:

"Clinical Aspects of Recidivism from the Viewpoint of the Lawyer and the Psychiatrist."

"The Problem of 'Diminished Responsibility'."

"Determinants of Society's Attitude Toward Social Deviants."

The lectureship is held by Dr. Alastair W. MacLeod, Assistant Professor of Psychiatry at McGill University and prominent in the field of medico-legal psychiatry.

A more detailed notice of this meeting may be obtained by writing or phoning (SP 4-0512) the Department of Psychiatry, University of Manitoba.

Dressing Service for Manitoba Cancer Patients

As part of its welfare program, the Manitoba Division of the Canadian Cancer Society maintains a supply of dressings which are available on recommendation of the attending physician to any cancer patient not in hospital. A memorandum regarding this service is being sent to members of the medical profession in Manitoba.

This service is provided free of charge to any patient in the province, and is of particular value to those requiring substantial quantities of dressings over a period of time. The following materials are available from the Society:

3″ x 3″ Gauze Flats—Sterilized
3″ x 8″ Surgical Dressing Pads—Sterilized
6″ x 8″ Surgical Dressing Pads—Sterilized
8″ x 12″ Surgical Dressing Pads—Sterilized
Incontinent Pads (18″ x 24″—disposable)
Jelonet Gauze Dressings
Telfa Sterile Pads
Adhesive Eyelet Strips
Zinc Peroxide Deodorant

The 8″ x 12″ and 6″ x 8″ dressings are wrapped individually, each package containing gauze flats and cotton sponges.

Requests should be directed to the nearest local unit of the Canadian Cancer Society, or to the Manitoba Division, Canadian Cancer Society, 283 Colony Street, Winnipeg 1. The initial order must come from the physician and should give the following information: Patient's name and address; site of disease; name of patient's doctor; size and quantity of dressings required for a two week period; details regarding delivery. Repeat orders can be forwarded by the patient or his family.

If arrangements for pick up or delivery cannot be made by the patient's family, the dressings will be sent prepaid to the patient's home in a package labelled "Dressing Service."

During the twelve month period ended Sept. 30, 1958, dressings were supplied by the Society to 174 cancer patients in various parts of Manitoba.

American Goiter Association

A meeting of the American Goiter Association will be held on April 30th, May 1st and 2nd in the Drake Hotel, Chicago, Illinois. The program for the three-day meeting will consist of papers and discussions dealing with the thyroid gland, its physiology, pharmacology, pathology and therapy.

Social News

Reported by K. Borthwick-Leslie, M.D.

Quote from the Lancet, London, England.

Scientific research by Dr. Keith L. Moore, assistant professor of anatomy at the U. of M.—confirms what a number of us have secretly suspected for years. The caption reads: "City Test Reveals Some Men Aren't"—Concise and clear, eh what?

Dr. Moore is being congratulated by the Lancet for his excellent work on "sex reversal" and his report to the profession. May we add our congratulations.

♦

Very interesting along different lines was Dr. Geo. LaFleche's account of his trip to Montreal as Vice President of the recently revived Beaver Club. Gisele MacKenzie took an active part in the revival procedure of the 1785 Beaver Club.

The description of the banquet, January 10th, of grilled buffalo steak, wild rice, oysters, red wine from oak casks, antique silverware, 18th century costumes, etc., sounds fabulous.

♦

The Winnipeg Clinic announce that David D. Gellman, M.D., M.B., B.S., M.R.C.P. (Lond.) and Glen A. Lillington, B.Sc., M.D. (Man.), M.S., recently associated with the Mayo Clinic have joined the Dept. of Internal Medicine.

♦

Dr. Gerard Allison brings back greetings from so many of our friends in Vancouver, and reports a most successful and enjoyable meeting there. My own personal messages were from Andy Turnbull, Ward Turvey, Harry Grieve, etc. Love to hear from them.

♦

The wedding of great interest to all: Josephine Hannah Morgan to Dr. Frank Burton Walsh, of Baltimore, Maryland will take place February 3rd, in Crescent Fort Rouge United Church — but more anon. I understand that M. R. MacCharles unexpectedly stepped out of his usual role of scalpel tossing to that of dart throwing, impersonating Cupid, and with his usual unerring aim as proven.

Dr. and Mrs. Emmet Dwyer, 118 Chataway Blvd., entertained Thursday for the bridal party of their daughter Moira and Joseph MacDonald, Charlottetown, P.E.I., which took place Saturday, Jan. 31st.

♦

Dr. and Mrs. Gordon M. Stephens announce the engagement of their daughter Winnifred Anne to John Charles MacKelvie. The wedding will take place February 14th at 5 p.m., in St. Andrews River Heights United Church.

♦

Mr. and Mrs. Allan L. Heath of Longueuil, Que. announce the engagement of their only daughter, Joyce Marlyn to John David Alexander Borthwick-Leslie, son of Dr. K. Borthwick-Leslie, Fort Garry, Man. and Dr. Walter Leslie, Halifax, N.S. The wedding will take place February 14th, at 3 p.m. in Gardenville United Church, Longueuil, Que.

Who is in a tailspin trying to get ready to leave for Montreal February 6th? However, not seeming to blow my own "Tug Boat Annie" horn, I did throw a darned good reception "in absentia" and cocktail party in honor of the kids. Thanks to all the good friends who took part.

♦

Welcome to John Steven Burke, born to Dr. and Mrs. M. E. Burke on Nov. 29, 1958 — baby brother for David Lewis.

♦

Dr. and Mrs. Donald M. Whitley announce the arrival of Mark Donald at the Royal Jubilee Hospital, Victoria, B.C., January 24, 1959.

♦

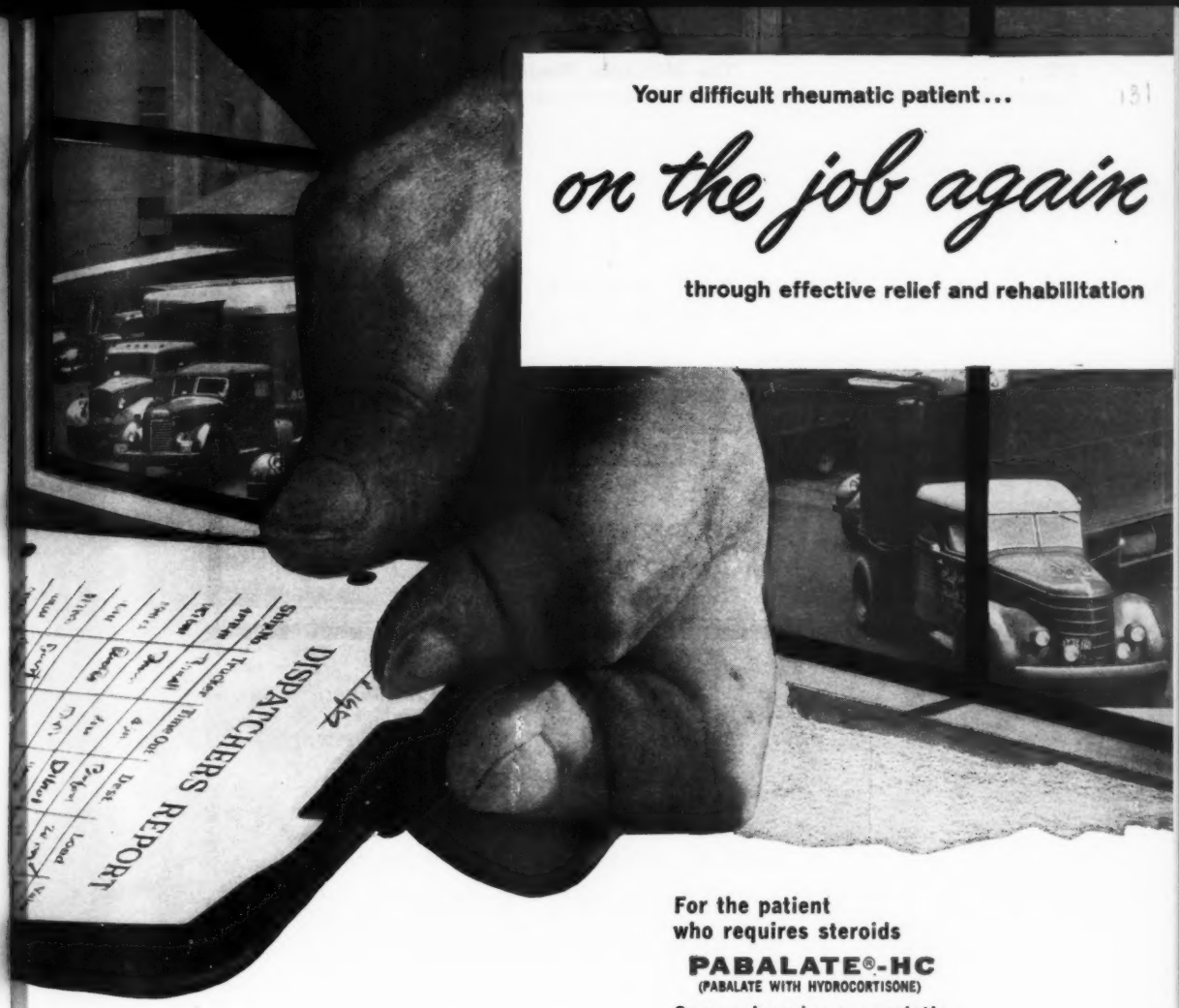
Dr. and Mrs. Noel Cutler announce the birth of David Lawrence, Dec. 6, 1958.

♦

Dr. and Mrs. Walter Zingg also welcome their son, David Walter, December 28, 1958, brother for Claudia, Jeannette and Esther. Thank you for the note, Dr. Zingg.

♦

Be seeing you with reports from our Eastern friends later on this month.



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Reciprocally acting nonsteroid antirheumatics . . . more effective than salicylate alone.

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Sodium para-aminobenzoate .....0.3 Gm. (5 gr.
Ascorbic acid .....50.0 mg

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Comprehensive synergistic combination of steroid and nonsteroid antirheumatics... full hormone effects on low hormone dosage . . . satisfactory remission of rheumatic symptoms in 85% of patients tested.

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DEPARTMENT OF HEALTH & PUBLIC WELFARE

COMMUNICABLE DISEASE PICTURE

LIST OF DEATHS FROM COMMUNICABLE DISEASES
December, 1958

URBAN: Cancer, 74; Diarrhoea and Enteritis, 2; Jaundice (infectious), 1; Pneumonia Lobar (490), 3; Pneumonias (other forms), 22; Septicaemia and Pyaemia, 1; Tuberculosis, 2. Other deaths under 1 year, 18. Other deaths over 1 year, 187. Stillbirths, 11. Total, 321.

RURAL: Cancer, 23; Diarrhoea and Enteritis, 3; Influenza, 1; Pneumonia Lobar (490), 4; Pneumonias (other forms), 8; Syphilis, 1. Tuberculosis, 4. Other deaths under 1 year, 14. Other deaths over 1 year, 192. Stillbirths, 20. Total, 270.

INDIAN: Diarrhoea and Enteritis, 3; Influenza, 1; Pneumonias (other forms), 5. Other deaths over 1 year, 5. Stillbirths, 1. Total, 15.

General

The poliomyelitis epidemic has now died out — the total for the year being 148 cases, of which 106 were paralytic and 42 non-paralytic. There is a continuing epidemic of scarlet fever and mumps in the Winnipeg area. The communicable disease picture for the year shows nine cases of diphtheria, two of which died. There were 378 cases of diarrhoea and enteritis under one year with 51 deaths, many of these cases occurring in the area north of 53. There were 736 cases of infectious hepatitis. We feel there is better reporting of this disease due to the use of gamma globulin for familial contacts as a means of prevention. 875 cases of scarlet fever were reported as against 121 in 1957. As previously mentioned there has been a scarlet fever epidemic in the Winnipeg area during the past several months. There were 465 cases of tuberculosis with a death rate of 4.7 per 100,000 compared with 5.9 the previous year.

North of 53 District

Two cases of poliomyelitis and 17 cases of diarrhoea and enteritis under one year were reported from this area. Most of these however were cases which had occurred previously and had not been reported.

Northern District

Eight cases of influenza were reported. It is not known if any of these cases were verified by laboratory examination.

Northwestern District

Thirty-one cases of mumps were reported.

Winnipeg District

Five cases of poliomyelitis were reported. These were all late reports as the most recent date of onset was in October. The epidemic of scarlet fever continues, 208 cases being reported. There were 301 cases of mumps. One case of diphtheria was reported.

Brandon District

Forty-one cases of measles, more than one-half the total reported in the province. There were also 101 cases of mumps.

Central District

Fourteen cases of scarlet fever were reported from this area.

Southern District

Eighty cases of scarlet fever were reported. The largest number from any one area being in the Rural Municipality of Franklin. Only one case of scarlet fever had been reported the previous month.